Costs, quality of life and cost-effectiveness of nutrition in gastrointestinal surgery

Document status and date:
Published: 01/01/2021

DOI:
10.26481/dis.20210125mp

Document Version:
Publisher's PDF, also known as Version of record

COSTS, QUALITY OF LIFE AND COST-EFFECTIVENESS OF NUTRITION IN GASTROINTESTINAL SURGERY

Madhuri Pattamatta

COLOFON

COSTS, QUALITY OF LIFE AND COST-EFFECTIVENESS OF NUTRITION IN GASTROINTESTINAL SURGERY, Madhuri Pattamatta
ISBN: 9789464191011

Cover design and layout by Anna Bleeker, persoonlijkproefschrift.nl
Printing: Gildeprint Enschede, gildeprint.nl

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Dissertation

to obtain the degree of Doctor at the Maastricht University,
on the authority of the Rector Magnificus,
Prof. Dr. Rianne M. Letschert
in accordance with the decision of the Board of Deans,
to be defended in public
on Monday 25 January 2021, at 16:00 hours

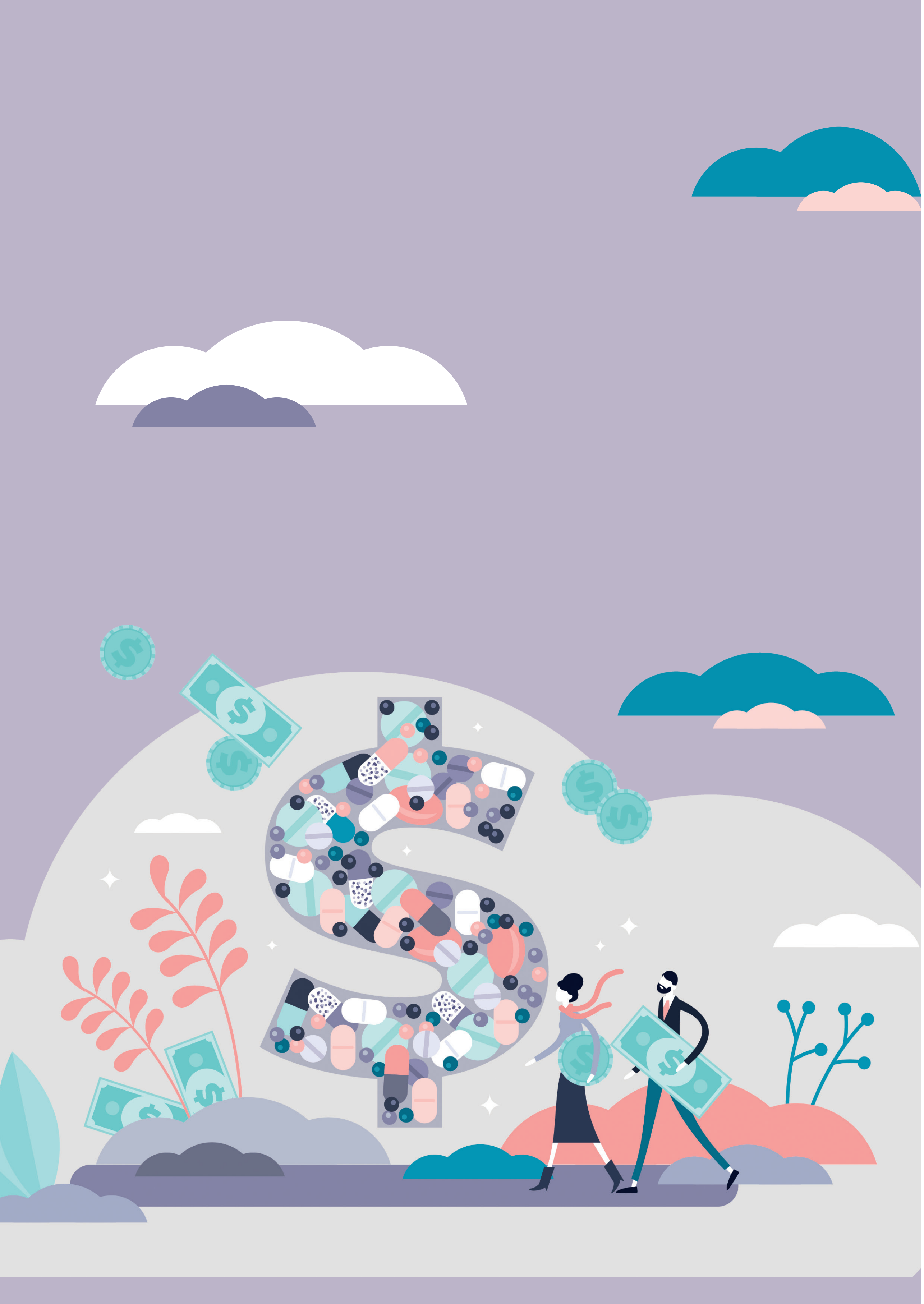
by
Madhuri Pattamatta

Supervisors:
Prof. Dr. Mr. Silvia Evers
Dr. Mickael Hiligsmann

Co-supervisor:
Dr. Misha Luyer

Assessment Committee:
Prof. Dr. Milena Pavlova (chair)
Prof. Dr. Wim Groot
Prof. Dr. Annemie Schols
Dr. Mark Nuijten
Dr. Karen Freijer

CONTENT



CHAPTER 1

General introduction

1.1. INTRODUCTION

Healthcare expenditures have been increasing rapidly in the Netherlands in the recent past. Major factors that drive healthcare spending are development and implementation of new expensive medical technologies, intensification of treatment and care and rising cost prices.[1] In order to efficiently allocate scarce resources, policymakers are interested in the relative (cost-) effectiveness of medical interventions to ensure optimal priority setting. As a result, economic evaluations are increasingly important in healthcare decision making.

This dissertation reports on health economic studies of perioperative nutritional interventions in colorectal cancer (CRC) and esophageal cancer (EC). The first chapter opens with some background information on CRC and EC. Then, a brief description of recent randomized controlled trials (RCT) that investigate the effect of perioperative nutritional care on postoperative recovery is presented. The rationale and methods for economic evaluation and previous economic evaluations of nutritional care on CRC and EC patients are then discussed. Finally, the objectives and outline of this thesis are presented at the end of this chapter.

1.2. GASTROINTESTINAL CANCERS

1.2.1. Clinical and economic burden

CRC and EC are the most common and important cancers among gastrointestinal cancers.

Colorectal cancer (CRC)

More than 90% of CRC cases occur in people aged 50 or older.[2] CRC is the second leading cause of cancer mortality and the third most common cancer worldwide.[3] CRC impair the quality of life of patients with substantial symptoms such as abdominal pain, change in bowel movement, blood loss and anaemia, fatigue and weight loss. Furthermore, treatment brings upon a burden to quality of life by means of surgery, chemo- and radiotherapy. In the Netherlands, 76,488 people were suffering from CRC in 2017 and 5,154 deaths were attributed to CRC in 2016,[4, 5] suggesting an even higher incidence of CRC than in other Western European countries.[6] CRC also represents a substantial economic burden for society. In 2017, in the Netherlands, annual healthcare costs of CRC were about 597 million euro, representing 0.7% of the total expenditure on the Dutch healthcare, and nearly 87% of these total costs were attributed to hospital costs.[7]

Esophageal cancer (EC)

EC is the sixth leading cause of cancer mortality and the eighth-most common cancer worldwide and has a poor prognosis.[3] The quality of life is largely affected by the obstructing nature of the tumour and also by the complex treatment which may include chemotherapy or chemoradiotherapy in combination with surgical resection.

First clinical presentation of the disease often includes symptoms such as dysphagia, eating difficulties and appetite loss resulting in considerable weight loss and fatigue, and decreased quality of life and daily living. There is a rising incidence in EC in the Netherlands.[8] with 5,467 people suffering from EC in 2018[9] and around 2,498 new cases identified in 2017.[10] The Dutch healthcare costs for EC were 124 million euro for both men and women in 2007.[1] This constitutes 0.17% of the total expenditure on the Dutch healthcare. Furthermore, CRC and EC patients have a high risk to suffer from disease related malnutrition due to changes in the metabolism induced by the disease. This can negatively influence the treatment and overall costs. The risk of postoperative complications also increases with a compromised nutritional status.[11-13]

1.2.2. Clinical management

Several studies have suggested that multimodality treatment consisting of (neo) adjuvant chemotherapy, radiotherapy and surgery are the most effective treatment options for both EC and CRC.[14-16]

Surgical colorectal resection is a common treatment where the part of the colon and/ or rectum that contains the tumour is removed. Surgery for colon cancer is usually followed by adjuvant chemotherapy in case of node-positive disease. For rectal cancer, patients may be pre-treated with (neoadjuvant) radiotherapy or chemoradiotherapy. In case of EC, esophagectomy which is surgical resection of some or most of esophagus is a common treatment. Many advances have been made over the years focused on improving cancer-specific and overall survival, such as the introduction of neoadjuvant chemoradiotherapy[17], transthoracic lymphadenectomy[18] and advances in chemotherapy regimens.

Despite advances in surgical techniques and improvements in perioperative care, such as minimally invasive surgery and enhanced recovery after surgery (ERAS) programs, the incidence of postoperative complications following colorectal and esophageal surgery remains substantial.[19-21] For EC, anastomotic leakage and pulmonary complications are the main factors for postoperative morbidity. [22, 23] Postoperative ileus (POI) and anastomotic leakage (AL) are major complications after colorectal surgery[19-21] and occur in 30-46% of the patients[24] leading to significant healthcare costs.[25] Postoperative complications lead to a significant increase in the use of hospital resources such as laboratory and diagnostic tests, surgical reoperations and intensive care unit (ICU) stay. Rising expenses for complex medical procedures combined with limited resources represent a major challenge. In a study by Straatman et al.[26], to assess the costs associated with complications after major abdominal surgery, major complications occurred in around twenty percent of patients and these patients account for more than 50% of the total costs.[26] Another study by Volanthen et al. demonstrates that postoperative complications are the major indicator of costs and they directly impact in-hospital costs.[27] Furthermore, postoperative complications negatively impact the short- and long-term quality of life.[22, 23, 28-32]

ERAS protocols entail a combination of strategies such as early mobilization, limitation of surgical drains and most importantly early initiation of oral intake. Early start of enteral nutrition is an essential part of the ERAS program and has been shown to improve recovery.[33] In the Netherlands, as in most European countries, oral intake is generally initiated 5 to 7 days after esophagectomy and oral intake is started directly after colorectal surgery. Studies have proven that there is no advantage of keeping the patient fasted after colorectal or esophageal surgery.[34, 35] Early feeding reduces both the risk of infection and the length of hospital stay. Furthermore, early enteral nutrition has been shown to reduce POI and AL in rectal surgery.[36] Previous studies have also proven that enteral nutrition reduces POI by reducing the inflammatory response via a mechanism that involves stimulation of the autonomic nervous system.[37] It remains unclear what the best strategy is for postoperative diet protocols in the early postoperative phase following surgical treatment.

Perioperative nutritional support has been introduced in many guidelines including ERAS. It is considered as a critical determinant in the outcomes of gastrointestinal surgery[38] and has been shown to improve clinical outcomes and to reduce costs. Optimization of perioperative care by introduction of minimally invasive surgery, ERAS programs and patient prehabilitation is promising, suggesting a positive effect on clinical consequences.

1.2.3. Recent RCTs

Three new trials, SANICS I, SANICS II and NUTRIENT II were recently conducted by our group to investigate the clinical and economic effects of perioperative nutritional care on recovery following the surgical procedure.

1. *A RCT to assess the effect of gum chewing on POI and inflammation in colorectal surgery (SANICS I trial).* In this RCT, the impact of gum chewing on postoperative complications (POI) was studied.[21] The trial proposed a simple and safe treatment where the patients were asked to chew gum before and after colorectal surgery to reduce POI and fasten recovery. Activation of the autonomic nervous system via the vagus nerve, which in turn brings a reduction in the systemic inflammation, was the main hypothesis in this trial. The trial compared the gum chewing group with the dermal patch (control group) which was placed on the lumbar back region 3 hours before surgery until the postoperative nutrition was initiated. The results of the trial report a reduction in the occurrences of POI and systemic inflammatory markers in the gum chewing group.[21]

2. Perioperative lipid-enriched nutrition versus standard care in patients undergoing elective, colorectal surgery (SANICS II): an international, multicentre, double-blinded

RCT was conducted in six hospital units in the Netherlands and Denmark.[39] The trial investigated the effect of perioperative lipid-enriched enteral nutrition on the postoperative inflammation and complications when compared with standard care in patients undergoing colorectal surgery. Enteral nutrition was administrated before the start of the surgery, continued during the operation and was stopped six hours after the end of the surgical procedure. After this, the patients were offered oral intake following ERAS guidelines. The hypothesis of the trial was similar to the SANICS I trial to demonstrate the stimulation of the autonomic nervous system via the vagus nerve. The trial results, however, reported that perioperative enteral nutrition does not further improve the clinical outcomes when compared to modern practices in colorectal surgery.[39]

Gum chewing (sham feeding) and perioperative enteral nutrition are both examples designed to accomplish vagus nerve stimulation and achieve early recover after colorectal surgery.[21, 39]

3. Nutritional route in esophageal resection trial II (NUTRIENT II)[40] is a multicentre open-label RCT performed at two hospitals in the Netherlands and one hospital in Sweden. The trial aimed to investigate the effects of direct oral intake versus start of oral intake on postoperative day 5 on postoperative functional recovery following minimally invasive esophagectomy. Early start of oral intake is a critical part of ERAS protocols and beneficial in most types of gastrointestinal surgery. The feasibility and safety of such a nutritional protocol following esophagectomy was studied in the NUTRIENT I trial. The NUTRIENT II trial showed that direct oral intake following esophagectomy resulted in a similar time to functional recovery and did not result in an increase of severity of postoperative complications.[41]

Even though the clinical effects of these interventions are limited, it is important to assess economic implications of the interventions. Cost-effectiveness analyses help decision makers to efficiently allocate healthcare resources and are nowadays playing an increasing role in pricing and reimbursement decisions. Furthermore, it is important to investigate the societal costs of such interventions, that in some specific surgical patients with higher inflammatory response, could be largely beneficial.

1.2.4. Health economic studies

Economic studies (such as the burden of disease and economic evaluations) are becoming increasingly important in our healthcare system to promote more rational use of health resources.

Burden of disease

A burden of disease study focuses on the cost of illness and quality of life of a disease over a defined period of time.[42] They could provide useful material relevant to current policy debates about resource allocation and research priorities.[43] Cost data also provide inputs for inclusion in cost-effectiveness analyses used in promoting efficient healthcare.[42]

In economic studies, costs are identified in the following categories:[44] A) Healthcare costs: These include all the costs in the healthcare sector including hospitalizations, medical procedures, and medications and all other costs during the study follow-up such as prevention, diagnostics, therapy and rehabilitation costs. B) Patient and family costs: These include informal care costs, travel and time costs. C) Costs in other sectors: These include the productivity costs due to absence or inefficiency at paid and unpaid work, police and legal costs, special education and counseling. Resources can be measured using cost diaries or cost questionnaires. These measurement tools are especially important in measuring the costs outside the healthcare sector, as there may not be a database containing this type of information. The Dutch healthcare Institute has published the Guideline for Cost Research in the Netherlands for application of standardized costing methodology.[45] The guideline also includes the reference prices for the common healthcare resources. The outcome of economic evaluation is typically expressed in QALY (quality-adjusted life years) that represents the impact of both quantity and quality of life. Utility measures are used to calculate QALYs and can be determined using preference based instruments such as EQ-5D.

Economic evaluations

An economic evaluation compares both the costs and effects of two or more interventions in a systematic manner which helps to evaluate the treatment that is more efficient.[46] There are two methods to conduct an economic evaluation: trial-based economic evaluation and model-based economic evaluation.

In a trial-based economic evaluation, all the costs and effects data are measured simultaneously alongside the trial. It provides thus an early opportunity to produce estimates of cost-effectiveness. The results of this approach reflect data from actual patients. Most importantly, a trial-based economic evaluation entails to the collection of patient level data (for example, duration of hospital stays and types and quantities of services used over the follow-up period of the trial), and the internal validity of the data can be assessed through controlled clinical conditions. The perspective of the trial influences the categories of resource use that are included in the study. Dutch guidelines prescribe a societal perspective, which implies that all significant costs and benefits need to be included in the analyses regardless of where this fall.

Trial-based economic evaluation require the collection of resource use data from sources such as medical records, separate patient questionnaires or interviews with health professionals. The valuation of the resource use requires estimation of the unit cost for each element of resource use consumed by the patient. The unit costs tend to be standardized across patients and trial centers. Apart from costs, consequences or outcomes of the alternatives should be examined in a trial-based economic evaluation. Outcome measures incorporated in a trial-based economic evaluation range from health endpoints (for example, hospital episodes avoided) to quality of life measures such as QALY.

Trial-based economic evaluation can be expressed as cost-effectiveness analysis and cost-utility analysis. In a cost-effectiveness analysis, outcomes are measured in natural units such as "length of hospital stay" or "change in occurrences of postoperative complications". Hence, the outcomes are easily measured and interpreted in clinical practice. In a cost-utility analysis, which is the preferred type of trial-based economic evaluation, outcomes are measured in terms of health state preference weights or utility weights. The most common example of health utility is QALY. Despite some limitations of the trial-based economic evaluations such as inability to generalize the treatment pathways and patient samples to larger populations[47], they provide relevant information by comparing the costs and consequences of alternatives.

Results of economic evaluation

To determine if a certain intervention is cost-effective, it is essential to calculate the incremental cost-effectiveness ratio (ICER). The extra costs that an intervention imposes over another are compared with the extra additional effects it brings. The additional costs and effects of intervention compared to control are determined using the following formula.

$$\frac{Costs_{Intervention\ group} - Costs_{Control\ group}}{Effects_{Intervention\ group} - Effects_{Control\ group}} = \frac{\Delta \mathrm{C}}{\Delta \mathrm{E}} = \frac{C}{E}$$

Where *Costs* $_{intervention\ group}$ and *Costs* $_{control\ group}$ represent the total costs during the period of the study and *Effects* $_{intervention\ group}$ and *Effects* $_{control\ group}$ represent the effects at the end of the follow-up.

For a graphical representation of the ICER, cost-effectiveness planes are commonly used to plot the costs against health effects. Costs are plotted on the y-axis and effects on the x-axis. A slope passing through the origin represents ICER. The cost-effectiveness plane is divided into four quadrants (see Figure 1). When the intervention is more effective and less costly than the comparator, the ICERs lie in the southeast quadrant and the intervention is considered dominant. Conversely, when the intervention is less effective and more costly, the ICERs lie in the northwest quadrant and the intervention is considered inferior. When the intervention is more costly and yet more effective, the ICERs lie in the northeast quadrant and when intervention is less costly and less effective, the ICERs lie in the southwest quadrant. Treatment is cost-effective when it is dominant. The implementation of a new treatment depends on the maximum amount of money that society is willing to pay for a gain in effectiveness, which is termed the 'threshold' or 'ceiling-ratio'.

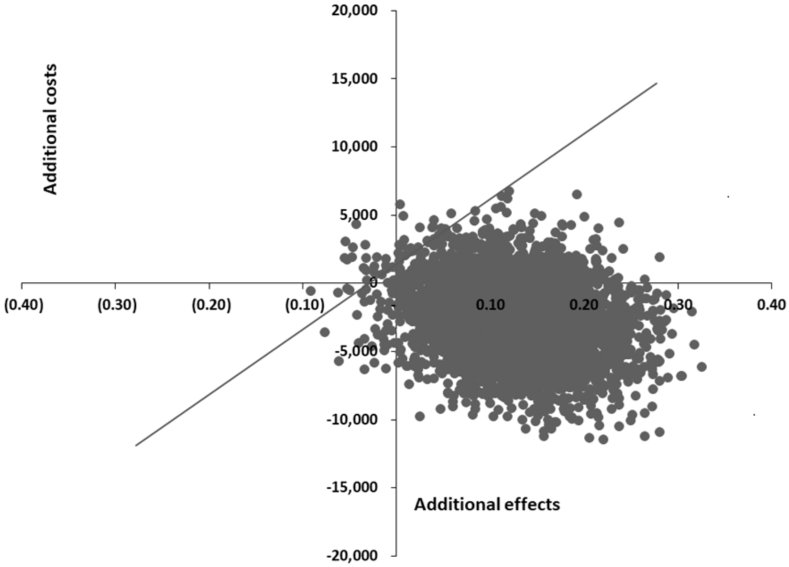


Figure 1. Example of a cost-effectiveness plane including fictional threshold.

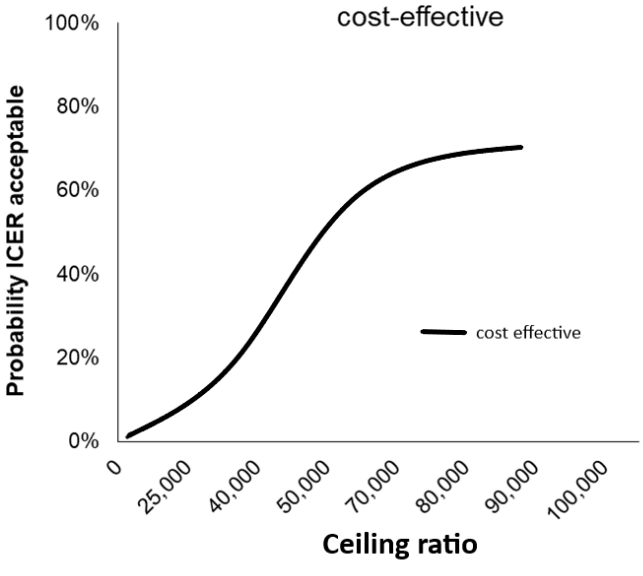


Figure 2. Example of a cost-effectiveness acceptability curve. ICER, incremental cost-effectiveness ratio.

Furthermore, cost-effectiveness acceptability curves (CEAC) can be calculated which show that the probability that the treatment is cost-effective, given different ceiling ratios (Figure 2). Bootstrapping is a method used to investigate the uncertainty surrounding ICER. Bootstrapping is a simulation technique where a large number of new samples N (usually 5000 times) are created with replacement from the original sample. This results in N different samples with each different ICER. ICERs are plotted on a CE plane to visualize the uncertainty around ICER. Additionally, 95% confidence interval can be calculated using the 2.5th and 97.5th percentile.

Although it is trivial to study the impact of interventions on the population, it is also of great significance to determine the role of different interventions to other socially desirable goals such as patient's quality of life and reducing the societal costs.

1.2.5. Economic studies in CRC and EC

Previous studies have demonstrated a rising global burden of CRC.[48-52] A study by Hall et al. showed a mean 15-month healthcare costs for CRC at £12,643 (€14,685) per patient and the majority of costs occurred at the primary treatment phase.[48] An Asian study estimated direct medical costs at 24.81%, direct non-medical care costs at 38.04% and indirect costs at 37.14% of the total cost.[49] Previous studies on health-related quality of life in CRC showed a utility of 0.67 during 0-6 months after diagnosis[51] and 0.76 during 1 year after diagnosis.[52] However, variations in valuation methodology and cost estimation time frame were evident in these studies. Similarly the burden of esophageal carcinoma is expected to rise significantly and to continue to increase due to the growth and aging of the population. A study by Thein et al. demonstrated that costs were highest in the terminal phase and inpatient hospitalization cost was the greatest contributor to total costs.[53]

Few studies have examined the clinical and economic effects of various nutritional interventions in CRC/EC surgery. A study by Atkinson et al., comparing the gum chewing (starting one day after surgery) with standard care found no differences in net monetary benefit between the groups and concluded that gum chewing was not cost effective.[54] In another retrospective analysis by Rinninella et al., patients were consequently enrolled in an intervention group (ERAS +Nutricatt protocol) and were compared to patients treated with standard ERAS protocol is. Nutricatt protocol consisted of nutritional prehabilitation before surgery and in the preoperative period. This study showed a significant decrease in the hospital costs, complications associated costs and length of stay in the intervention group were found.[55] A previous study by Sun et al evaluating the impact of early oral feeding on postoperative complications following minimally invasive esophagectomy concluded that early oral feeding was non-inferior compared to the standard care and had an improved short term quality of life. However, there is a large variation between studies with regards to timing of interventions, control group definitions, clinical outcomes, cost perspective, the composition of nutritional supplements which make it difficult to interpret and compare the results accurately.

New trials were conducted (SANICS 1, SANICS II, and NUTRIENT II) by our team with new interventions and it is essential to conduct economic evaluations of the new trials to generate more evidence and achieve clear conclusions.

1.3. OBJECTIVES OF THIS THESIS

Given the increasing burden of CRC and EC and the importance of economic considerations, this study aims to get insight into various aspects of economic analysis including the burden of disease and assessment of the cost-effectiveness of recent advances in the treatment of CRC/EC. More specifically, this thesis will compose of two parts:

1. To estimate the burden of preoperative CRC in terms of cost and quality of life and explore the burden of the postoperative complications of CRC. (Part I: Cost of illness/ burden of disease studies)
2. To assess the cost-effectiveness of the interventions tested in the three trials previously described: SANICS I, SANICS II and NUTRIENT II trials. (Part II: Economic evaluations)

1.4. OUTLINE OF THIS THESIS

To answer the first objective of the thesis, in **chapter 2**, Data on the preoperative societal burden of CRC and quality of life of the SANICS II trial population is provided. In **chapter 3**, postoperative complications following colorectal surgery in terms of clinical inflammation, quality of life and costs are being explored answering the first objective of the thesis.

With regard to the second objective of this thesis, the next 3 chapters, chapters 4 to 6 are focused on economic evaluations. **chapter 4** describes the design and cost-effectiveness results of gum chewing for patients undergoing colorectal surgery. The study was conducted under a hospital perspective where the costs and effects of gum chewing were compared to standard care in patients undergoing colorectal surgery. Furthermore, health-related quality of life between the two treatment arms was compared. In ***chapter 5,*** the results of the trial-based economic evaluation of the SANICS II study are presented. The cost-effectiveness and cost-utility analysis of perioperative enteral nutrition compared to standard care in patients undergoing colorectal surgery were described. A societal perspective was adopted and quality of life comparisons between the groups was additionally analyzed. **chapter 6** gives insight into the hospital costs and quality of life changes in patients undergoing esophagectomy using the data from the NUTRIENT II trial.

Finally, **chapter 7** provides elaborate answers to the research questions addressed and discusses the merits and demerits of the research performed in this thesis.

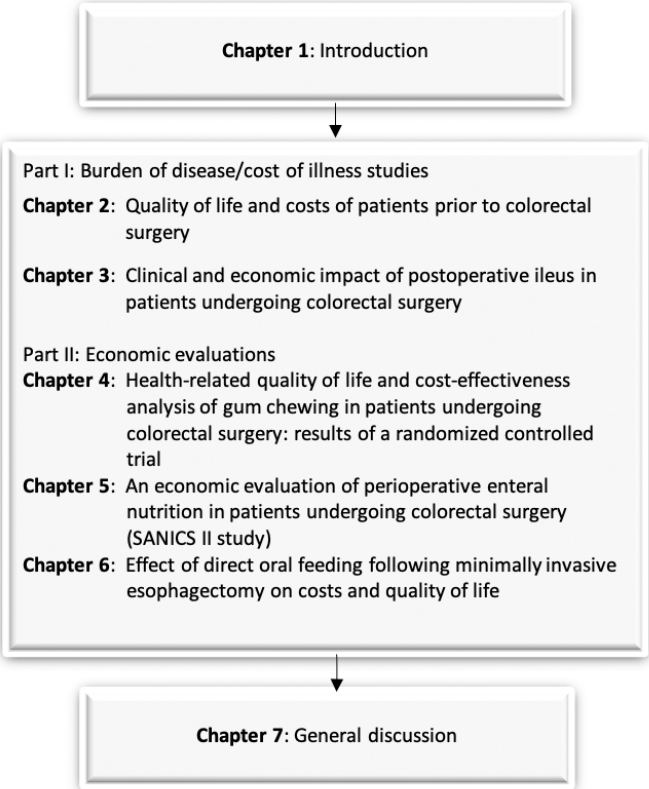


Figure 3. Outline of the thesis.

REFERENCES*:*

1. Slobbe LCJ SJ, Groen J, Poos M.J.J.C KG. Kosten van ziekten in Nederland 2007: Trends in de Nederlandse zorguitgaven 1999-2010. RIVM Rapp 270751023. 2011;28-12-2011. 2008.
2. National Institutes of Health What You Need To Know About Cancer of the Colon and Rectum. Bethesda, MD: U.S. Department of Health and Human Services & National Institutes of Health. 2006.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
4. kankerregistratie N. [Available from: https://www.cijfersoverkanker.nl/selecties/Dataset_5/img5c45ac75b02b2?
5. KWF. https://www.kwf.nl/kanker/dikkedarmkanker/Pages/default.aspx [
6. Ferlay J. Cancer Incidence in Five Continents. Processing of data. IARC Sci Publ. 1992(120):39-44.
7. Volksgezondheidenzorg.info. https://www.volksgezondheidenzorg.info/onderwerp/dikkedarmkanker/kosten/kosten#node-kosten-van-zorg-voor-dikkedarmkanker [
8. Dikken JL, Lemmens VE, Wouters MW, Wijnhoven BP, Siersema PD, Nieuwenhuijzen GA, et al. Increased incidence and survival for oesophageal cancer but not for gastric cardia cancer in the Netherlands. European journal of cancer (Oxford, England : 1990). 2012;48(11):1624-32.
9. Kankerregistratie N. Prevalentie slokdarmkanker 2018 [Available from: https://www.cijfersoverkanker.nl/selecties/Dataset_7/img5c5949073b787.
10. Incidentie slokdarmkanker [Internet]. KWF. 2020 [cited 28/07/2020]. Available from: https://www.kwf.nl/kanker/kwf-en-slokdarmkanker/Pages/default.aspx.
11. Weimann A, Braga M, Carli F, Higashiguchi T, Hübner M, Klek S, et al. ESPEN guideline: Clinical nutrition in surgery. Clinical nutrition (Edinburgh, Scotland). 2017;36(3):623-50.
12. Freijer K. Nutrition Economics - An Introduction: ISPOR CONNECTIONS 2014;4:10-11; July 2014 [Available from: https://www.ispor.org/member-groups/special-interest-groups/nutrition-economics.
13. Freijer K, Bours MJ, Nuijten MJ, Poley MJ, Meijers JM, Halfens RJ, et al. The economic value of enteral medical nutrition in the management of disease-related malnutrition: a systematic review. Journal of the American Medical Directors Association. 2014;15(1):17-29.
14. Kuipers EJ, Grady WM, Lieberman D, Seufferlein T, Sung JJ, Boelens PG, et al. Colorectal cancer. Nature reviews Disease primers. 2015;1:15065.
15. Ihnat P, Ostruszka P, Vavra P, Peteja M, Zonca P. Treatment strategies for patients with colorectal carcinomaand synchronous liver metastases. Rozhledy v chirurgii : mesicnik Ceskoslovenske chirurgicke spolecnosti. 2018;97(10):451-4.
16. Kato H, Nakajima M. Treatments for esophageal cancer: a review. General thoracic and cardiovascular surgery. 2013;61(6):330-5.
17. van Heijl M, van Lanschot JJ, Koppert LB, van Berge Henegouwen MI, Muller K, Steyerberg EW, et al. Neoadjuvant chemoradiation followed by surgery versus surgery alone for patients with adenocarcinoma or squamous cell carcinoma of the esophagus (CROSS). BMC surgery. 2008;8:21.

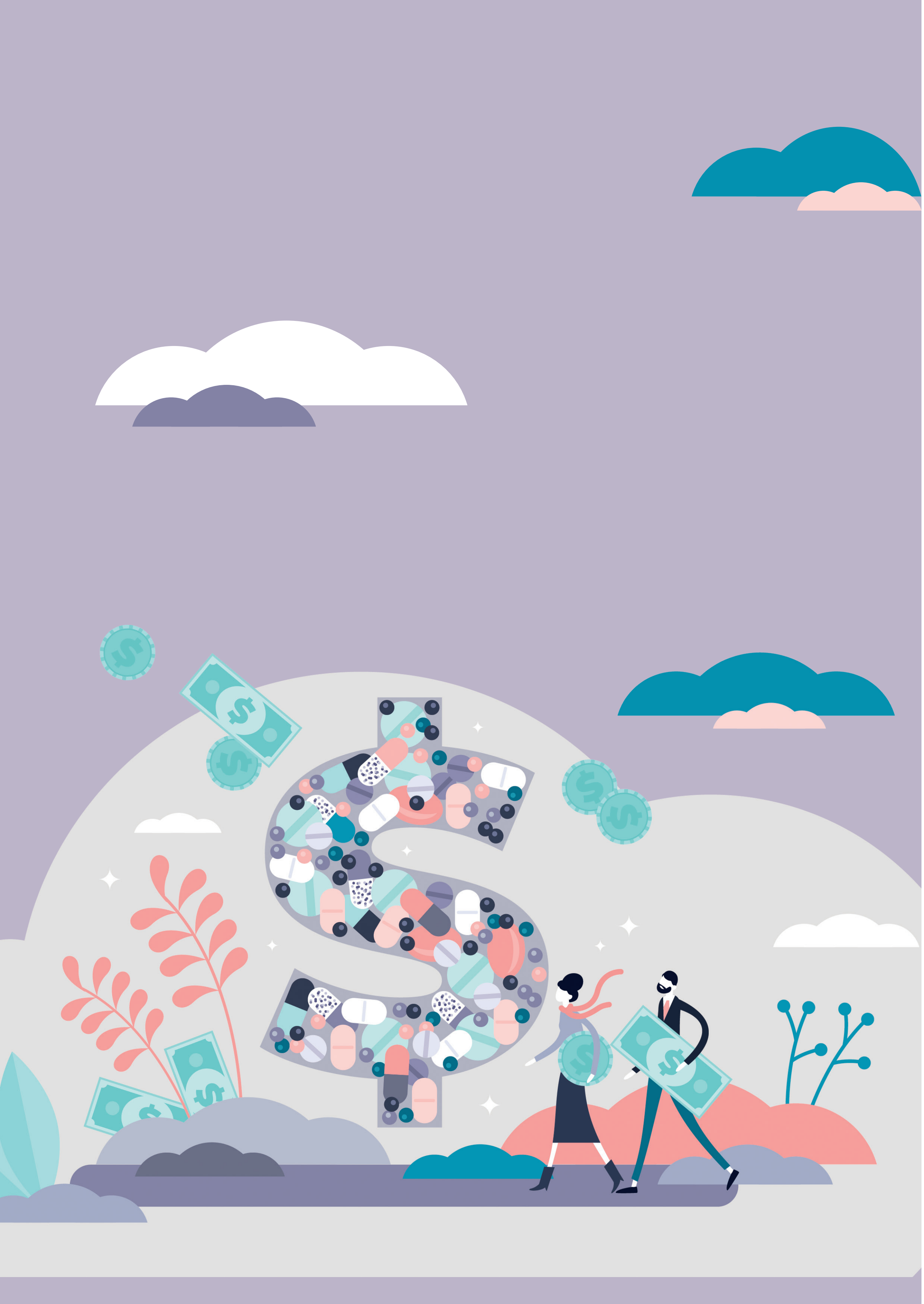
18. Hulscher JB, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. The New England journal of medicine. 2002;347(21):1662-9.
19. Spanjersberg WR, Reurings J, Keus F, van Laarhoven CJ. Fast track surgery versus conventional recovery strategies for colorectal surgery. The Cochrane database of systematic reviews. 2011(2):Cd007635.
20. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Br J Surg. 2015;102(5):462-79.
21. van den Heijkant TC, Costes LM, van der Lee DG, Aerts B, Osinga-de Jong M, Rutten HR, et al. Randomized clinical trial of the effect of gum chewing on postoperative ileus and inflammation in colorectal surgery. Br J Surg. 2015;102(3):202-11.
22. Goense L, van Dijk WA, Govaert JA, van Rossum PS, Ruurda JP, van Hillegersberg R. Hospital costs of complications after esophagectomy for cancer. Eur J Surg Oncol. 2017;43(4):696-702.
23. Carrott PW, Markar SR, Kuppusamy MK, Traverso LW, Low DE. Accordion severity grading system: assessment of relationship between costs, length of hospital stay, and survival in patients with complications after esophagectomy for cancer. Journal of the American College of Surgeons. 2012;215(3):331-6.
24. Wang J, Wei C, Tucker SL, Myles B, Palmer M, Hofstetter WL, et al. Predictors of postoperative complications after trimodality therapy for esophageal cancer. International journal of radiation oncology, biology, physics. 2013;86(5):885-91.
25. Short MN, Aloia TA, Ho V. The influence of complications on the costs of complex cancer surgery. Cancer. 2014;120(7):1035-41.
26. Straatman J, Cuesta MA, de Lange-de Klerk ES, van der Peet DL. Hospital cost-analysis of complications after major abdominal surgery. Digestive surgery. 2015;32(2):150-6.
27. Vonlanthen R, Slankamenac K, Breitenstein S, Puhan MA, Muller MK, Hahnloser D, et al. The impact of complications on costs of major surgical procedures: a cost analysis of 1200 patients. Annals of surgery. 2011;254(6):907-13.
28. Iyer S, Saunders WB, Stemkowski S. Economic burden of postoperative ileus associated with colectomy in the United States. J Manag Care Pharm. 2009;15(6):485-94.
29. Govaert JA, Fiocco M, van Dijk WA, Scheffer AC, de Graaf EJ, Tollenaar RA, et al. Costs of complications after colorectal cancer surgery in the Netherlands: Building the business case for hospitals. Eur J Surg Oncol. 2015;41(8):1059-67.
30. Barletta JF, Senagore AJ. Reducing the burden of postoperative ileus: evaluating and implementing an evidence-based strategy. World J Surg. 2014;38(8):1966-77.
31. Brown SR, Mathew R, Keding A, Marshall HC, Brown JM, Jayne DG. The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. Annals of surgery. 2014;259(5):916-23.
32. Bosma E, Pullens MJ, de Vries J, Roukema JA. The impact of complications on quality of life following colorectal surgery: a prospective cohort study to evaluate the Clavien-Dindo classification system. Colorectal Dis. 2016;18(6):594-602.
33. Lassen K, Soop M, Nygren J, Cox PB, Hendry PO, Spies C, et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. Archives of surgery (Chicago, Ill : 1960). 2009;144(10):961-9.

34. Andersen HK, Lewis SJ, Thomas S. Early enteral nutrition within 24h of colorectal surgery versus later commencement of feeding for postoperative complications. The Cochrane database of systematic reviews. 2006(4):Cd004080.
35. Berkelmans GHK, Fransen LFC, Dolmans-Zwartjes ACP, Kouwenhoven EA, van Det MJ, Nilsson M, et al. Direct Oral Feeding Following Minimally Invasive Esophagectomy (NUTRIENT II trial): An International, Multicenter, Open-label Randomized Controlled Trial. Annals of surgery. 2019.
36. Boelens PG, Heesakkers FF, Luyer MD, van Barneveld KW, de Hingh IH, Nieuwenhuijzen GA, et al. Reduction of postoperative ileus by early enteral nutrition in patients undergoing major rectal surgery: prospective, randomized, controlled trial. Annals of surgery. 2014;259(4):649-55.
37. Lubbers T, De Haan JJ, Hadfoune M, Zhang Y, Luyer MD, Grundy D, et al. Lipid-enriched enteral nutrition controls the inflammatory response in murine Gram-negative sepsis. Critical care medicine. 2010;38(10):1996-2002.
38. Sungurtekin H, Sungurtekin U, Balci C, Zencir M, Erdem E. The influence of nutritional status on complications after major intraabdominal surgery. Journal of the American College of Nutrition. 2004;23(3):227-32.
39. Peters EG, Smeets BJJ, Nors J, Back CM, Funder JA, Sommer T, et al. Perioperative lipid-enriched enteral nutrition versus standard care in patients undergoing elective colorectal surgery (SANICS II): a multicentre, double-blind, randomised controlled trial. The lancet Gastroenterology & hepatology. 2018;3(4):242-51.
40. Berkelmans GH, Wilts BJ, Kouwenhoven EA, Kumagai K, Nilsson M, Weijs TJ, et al. Nutritional route in oesophageal resection trial II (NUTRIENT II): study protocol for a multicentre open-label randomised controlled trial. BMJ open. 2016;6(8):e011979.
41. Weijs TJ, Nieuwenhuijzen GA, Ruurda JP, Kouwenhoven EA, Rosman C, Sosef M, et al. Study protocol for the nutritional route in oesophageal resection trial: a single-arm feasibility trial (NUTRIENT trial). BMJ open. 2014;4(6):e004557.
42. Segel JE. Cost-of-illness studies—a primer. RTI-UNC Center of Excellence in Health Promotion Economics. 2006:1-39.
43. RIVM. Draft guidelines for estimating expenditure by disease, age and gender under the system of health accounts (SHA) framework, N.I.f.P.H.a.t. Environment, Editor 2007 N.I.f.P.H.a.t 2007 [cited 2007.
44. Kanters TA, Bouwmans CA, van der Linden N, Tan SS, Hakkaart-van Roijen L. Update of the Dutch manual for costing studies in health care. PloS one. 2017;12(11):e0187477.
45. Nederland Z. Richtlijn voor het uitvoeren van economische evaluaties in de gezondheidszorg. Diemen; . 2015.
46. Rudmik L, Drummond M. Health economic evaluation: important principles and methodology. The Laryngoscope. 2013;123(6):1341-7.
47. Drummond M, Manca A, Sculpher M. Increasing the generalizability of economic evaluations: recommendations for the design, analysis, and reporting of studies. International journal of technology assessment in health care. 2005;21(2):165-71.
48. Hall PS, Hamilton P, Hulme CT, Meads DM, Jones H, Newsham A, et al. Costs of cancer care for use in economic evaluation: a UK analysis of patient-level routine health system data. Br J Cancer. 2015;112(5):948-56.
49. Byun JY, Yoon SJ, Oh IH, Kim YA, Seo HY, Lee YH. Economic burden of colorectal cancer in Korea. J Prev Med Public Health. 2014;47(2):84-93.

50. Farkkila N, Torvinen S, Sintonen H, Saarto T, Jarvinen H, Hanninen J, et al. Costs of colorectal cancer in different states of the disease. Acta Oncol. 2015;54(4):454-62.
51. Farkkila N, Sintonen H, Saarto T, Jarvinen H, Hanninen J, Taari K, et al. Health-related quality of life in colorectal cancer. Colorectal Dis. 2013;15(5):e215-22.
52. Ko CY, Maggard M, Livingston EH. Evaluating health utility in patients with melanoma, breast cancer, colon cancer, and lung cancer: a nationwide, population-based assessment. J Surg Res. 2003;114(1):1-5.
53. Thein H-H, Jembere N, Thavorn K, Chan KKW, Coyte PC, de Oliveira C, et al. Estimates and predictors of health care costs of esophageal adenocarcinoma: a population-based cohort study. BMC Cancer. 2018;18(1):694-.
54. Atkinson C, Penfold CM, Ness AR, Longman RJ, Thomas SJ, Hollingworth W, et al. Randomized clinical trial of postoperative chewing gum versus standard care after colorectal resection. Br J Surg. 2016;103(8):962-70.
55. Rinninella E, Persiani R, D'Ugo D, Pennestri F, Cicchetti A, Di Brino E, et al. NutriCatt protocol in the Enhanced Recovery After Surgery (ERAS) program for colorectal surgery: The nutritional support improves clinical and cost-effectiveness outcomes. Nutrition. 2018;50:74-81.

PART I

Burden of disease / cost of illness studies



CHAPTER 2

Quality of life and costs of patients prior to colorectal surgery

Published as:
Pattamatta M, Smeets BJJ, Evers SMAA, Peters EG, Luyer MDP, Hiligsmann M. Quality of life and costs of patients prior to colorectal surgery. Expert Review of Pharmacoeconomics & Outcomes Research. 2020 Mar;20(2):193-8. doi: 10.1080/14737167.2019.1628641.

ABSTRACT

Objective: To assess the quality of life and societal costs of patients prior to colorectal surgery in the Netherlands.

Methods: This study is embedded in a previous randomized controlled trial (SANICS II). The quality of life was measured using EQ-5D-5L questionnaires. The iMTA medical consumption questionnaire (iMCQ) and the iMTA productivity costs questionnaire (iPCQ) were used to identify and measure healthcare and productivity costs. Subgroup analyses were performed based on age and gender.

Results: A total of 178 patients were included in the cost analysis and a total of 161 patients in the quality of life analysis. The three-month mean societal cost per patient amounted to €3,211 of which €1,459 was due to productivity losses. The mean utility was 0.88 per patient. Gender was an important predictor in quality of life with men scoring significantly higher than women (0.92 versus 0.82) at $p < 0.0001$.

Conclusion: Colorectal cancer represents a high economic burden in the Netherlands. Further research with repeated cost and quality of life measurements would be needed to explore the change over time and the effects of surgery.

2.1. INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer (10% of the total) in men and second in women (9.2% of the total) worldwide.[1] The incidence of CRC is higher in the Netherlands when compared to other countries in Western Europe.[2] Nearly 15,427 new cases of CRC were reported in 2016 and the incidence has been steadily increasing at a rate of 13%-18% per year (1990–2016).[3] Prevalence of CRC is further expected to rise as a result of national CRC screening and ageing Dutch population.[4, 5]

Survival rates have increased in patients with CRC due to improvements in (neo) adjuvant treatment and surgical approaches.[6, 7] However, this is also accompanied with side effects including physical discomfort and difficulties in terms of life satisfaction[8], depression[9] and psychological distress[10] which may ultimately lower the quality of life. Additionally, CRC imposes a significant economic burden for the patient and society.[11, 12] The economic burden of CRC is determined by many different factors and to better focus on what items may be important, the burden of disease (BoD) studies assessing the quality of life and financial aspects of a particular disease over a defined period of time are essential.[13]

Cost elements in BoD studies include healthcare costs, patient and family costs and productivity losses among patients and caregivers. There is limited information about cost and quality of life on CRC[11, 12, 14] with very few or no studies from the Netherlands, especially the burden of CRC prior to surgery is largely unknown. To our knowledge, this is the first study to estimate the costs prior to colorectal surgery in the Netherlands. The aim of this study is, therefore, to estimate the societal costs and the quality of life of CRC patients prior to surgery. This study will further provide important results for future health economic analyses of new interventions in patients with CRC and increases the understanding of the CRC-related costs per patient in the interval between diagnosis and treatment.

2.2. METHODS

2.2.1. Study design

In this study, we estimated the costs in monetary terms and quality of life in utilities. Although other approaches are also well established, a bottom-up, prevalence-based approach from a societal perspective was used since this approach is considered as the most appropriate for assessing the cost of illness.[15] This study is embedded in the SANICS II trial which is a multicenter randomized controlled trial, the details of which are described elsewhere.[16, 17] In brief, the SANICS II study investigates the clinical effectiveness and cost-effectiveness of perioperative nutrition compared with standard care (nil by mouth) in patients undergoing colorectal surgery. In this study, we report costs and quality of life prior to colorectal surgery. Both the treatment arms were pooled for the purpose of this study.

2.2.2. Population and setting

Five hospitals (three hospitals from the Netherlands and two hospitals from Denmark) participated in the original trial. For this study, patients in Dutch hospitals only were included. Patients who are above 18 years of age and undergoing elective segmental colorectal resection with anastomosis were eligible for inclusion. Patients with previous gastric or esophageal resection, peritoneal carcinomatosis, pre-existent or creation of an ileostomy, steroid use, and use of medication that disrupts the acetylcholine metabolism were excluded. Furthermore, patients with the benign colorectal disease were excluded for this study. The medical ethics committee of Catharina Hospital (Eindhoven, the Netherlands) granted the approval for the original study. Written informed consent was obtained from all the included participants.

2.2.3. Data collection

Cost and quality of life were collected by means of questionnaires for the period between August 2014 and February 2017, at a single time point (baseline). The baseline questionnaires were handed out to the patients on the first day of their admission.

2.2.4. Cost perspective

The study followed the Dutch guidelines for health economic evaluations, which promotes cost calculation from a societal perspective meaning that all the healthcare costs and patient and family costs of CRC were accounted for.[18]

Cost estimation was followed in 3 steps namely:
1.Identification, 2. measurement and 3. Valuation.

Step I: Identification of costs:
Costs included were those related to preoperative CRC care and were categorized as 1. Healthcare cost (i.e. hospitalizations, medical procedures, medications etc.), 2.

Patient and family costs (i.e. Travel and time costs) and 3.Costs in other sectors (i.e. productivity costs). As there are no registrations available for time and travel costs, they were excluded.

Step II: Measurement of costs
Self-reported questionnaires for healthcare consumption and productivity losses were used in this study. The iMTA Medical consumption questionnaire (MCQ) was used to measure the healthcare utilization and the iMTA productivity cost questionnaire (PCQ) was used to measure the costs due to productivity losses in two domains related to 1) paid work due to absenteeism and presenteeism, and 2) unpaid work.[19] Both the questionnaires are commonly used in the Netherlands to assess healthcare and productivity losses. These questionnaires are generic and the items are not related to any specific disorder. The recall period for the MCQ is 3 months and for the PCQ is 4 weeks. The PCQ costs per patient were extrapolated to 3 months.

Step III: Valuation of costs
The costs were expressed and analyzed in Euros and were indexed for the year 2017. The updated Dutch Manual for Cost Analysis in Healthcare Research was used for the valuation of the healthcare costs.[18] The identified health services consumed by the patient were multiplied with their corresponding unit prices. Total costs were estimated by summing the individual services. All medication costs were derived from the website with the official listing of drugs with prices: www.medicijnkosten.nl. Medication costs were based on the price per dosage of the drug in the Netherlands. In case of uncertainty regarding a medication, the lowest cost price was used. Medications with out a specific name were omitted (for example, when a patient mentions antibiotics or ‘medicine for stomach protection’). Productivity losses were valued using the friction cost method which takes into account production losses confined to the period needed to replace the sick employee (85 days).[20] Friction costs were applied to patients below the retirement age.

2.2.5. Quality of life perspective
Quality of life was assessed using the Dutch five level, five-dimensional EuroQoL (EQ-5D-5L) questionnaire consisting of mobility, self-care, usual activities, pain/discomfort and anxiety/ depression. Each dimension was scored on a five-point scale which represented ‘no problems’, ‘slight problems’, ‘moderate problems’, ‘severe problems’ and ‘extreme problems’. The 5 dimensions can be summed into a health state. Utility values can be calculated for these health states, using preferences elicited from a general population, the so-called Dutch algorithm.[21]

2.3. STATISTICAL METHODS

All statistical analyses were performed using IBM SPSS Statistic V.24. For Windows (IBM corp., Armond, NY, USA). Since the cost data are typically highly skewed, non-parametric bootstrapping (with 5000 replications) was used to estimate the 95% confidence intervals around the mean difference in all the cost categories. Subgroup analyses were performed according to the gender (male and female) and median age (older age group is >67 years; younger age group is <67 years). Age and gender are two potentially important demographic characteristics and were available in our study. Estimates such as means, medians, standard deviation and confidence intervals were reported. Mann-Whitney U test was used to compare the cost means.

2.4. RESULTS

2.4.1.Demographic characteristics

A total of 184 patients participated in the RCT of which 178 patients completed the cost questionnaires and 161 patients completed the EQ-5D-5L questionnaires. This is a complete case analysis and therefore we did not have any missing data in this study. More than half of them were men (n = 104; 64.59%) and the mean age of the patients was 67.55 years (SD 9.55). The number of patients in the younger age group was slightly higher than in the older age group (83 versus 78).

2.4.2. Costs

The mean societal cost per patient amounted to € 3,211 over a period of 3 months of which 45.4% (€1,459) was due to productivity losses. (Table 1). Total healthcare sector costs represented 54.5% (€1,752) of the total societal costs of which hospitalizations at 23.9% (€420), visits to the outpatient clinic at 21.9% (€385) and treatment procedures at 20.8% (€365) were the main contributors (Table 1).

Table 1. Total resource use and costs (Euros) and Utilities

	Users			Resource use per patient		Cost per patient(€)			
	Unit	N	Percent	Mean	SD	Mean	SD	Median	95%CI
Healthcare costs									
General practitioner	Contact	121	67.97	1.62	2.25	53	80	33	[43, 66]
Medications	Various	122	68.53	-	-	107	269	9	[71, 149]
Outpatient clinic	Contact	151	84.83	4.8	4.51	385	345	320	[335, 436]
Allied health professionals	Contact	43	24.15	1.51	3.75	44	132	0	[27, 65]
Home care	Hour	18	10.11	4.26	19.05	149	779	0	[54, 277]
Hospital stay	Nightstay	36	20.22	0.93	3.01	420	1,336	0	[247, 633]
Emergency room visits	Contact	20	11.23	0.16	0.48	43	124	0	[26, 61]
Ambulance	Trip	7	3.93	0.06	0.37	41	231	0	[13, 79]
Diagnostics	Test	43	24.15	0.43	0.88	140	321	0	[96, 189]
Treatment	Procedure	25	14.05	0.12	0.33	365	1,209	0	[208, 556]
Total healthcare costs		178	100			1,752	2,583	854	[1,403, 2,147]
Productivity costs									
Paid home care	Hour	30	16.21	33.21	110.63	1,290	4,010	0	[743, 1,888]
Inability to do unpaid labor	Hour	24	12.97	12.44	46.28	168	730	0	[77, 285]
Total productivity costs		46	24.86			1,459	4,096	0	[894, 2,088]
Societal costs						3,211	5,008	1,164	[2,534, 3,936]
Utilities						0.88	0.15	0.90	

*SD, standard deviation; CI, confidence interval (2.5th percentile, 97.5thpercentile)

Patients stayed on an average 0.9 days in a hospital and had 1.5 consults with allied health professionals (e.g. physiotherapist, social worker). Patients were unable to perform paid labor for 33.2 hours (4.15days) and unpaid labor for 12.4 hours (1.55 days). Nearly 67.9% of patients used general practitioner services and 84.8% had outpatient visits. Seven patients (3.9%) used ambulance service and 20 patients (11.2%) had emergency visits to the hospital. Forty three patients (24.1%) had a diagnostic test and 25 patients (14%) had a treatment procedure per-formed in the three months prior to CRC surgery.

The younger age group showed societal costs at €4,449 compared to the older age group at €1,946 (p = 0.073). The mean general practitioner costs were significantly higher for the older age group (64 versus 43 at p = 0.014). Paid care and total productivity costs were also significantly higher for younger age group (2,548 versus 3 at p < 0.0001; and 2,752 versus 135 at p < 0.0001 respectively). The mean societal costs for men were €3,465 and that for women €2,759 with no statistical significance. Mean general practitioner care costs were significantly higher in women when compared to men (€74 versus €42) at p = 0.003. Mean home care costs were significantly higher for women (€263 versus €85) at p = 0.016 (Table 2)

2.4.3. Utilities

The mean utility was 0.88 (SD: 0.15) per patient prior to intervention and surgery. Men had a significantly higher utility when compared to the women (0.92 versus 0.82) at p < 0.0001. The utilities for the younger and older age groups were not different between the groups (0.90 versus 0.86 p = 0.86). With regards to pain/discomfort, 24.2% of the total patients experienced slight problems. The frequency of five dimensions as measured using EQ-5D-5L questionnaires is reported in Table 3.

Table 2. Costs (expressed in euros) and utilities of colorectal cancer patients according to gender and age

	Male		**Female**			**Age below 67**		**Age above 67**		
	Mean	SD	Mean	SD	P-value	Mean	SD	Mean	SD	P-value
Healthcare costs										
General practitioner	42	65	74	97	**0.003**	43	76	64	82	**0.014**
Medication	95	215	128	345	0.639	101	212	113	318	0.214
Outpatient clinic	380	349	394	341	0.745	379	357	390	334	0.562
Allied health professionals	41	138	50	122	0.672	39	121	49	143	0.386
Home care	85	650	263	963	**0.016**	106	759	193	801	**0.044**
Hospital stay	466	1,551	339	830	0.766	290	797	553	1,716	0.142
Emergency room visits	34	111	60	144	0.125	34	96	52	147	0.582
Ambulance	48	272	28	130	0.946	47	279	34	170	0.977
Diagnostics	112	231	190	434	0.635	172	383	108	239	0.261
Treatment	481	1,407	160	698	0.794	480	1,254	248	1,156	0.870
Total healthcare costs	1,787	2,784	1,690	2,201	0.513	1,696	2,309	1,810	2,849	0.411
Productivity costs										
Paid home care	1,506	4,458	904	3,050	0.664	2,548	5,361	3	29	**<0.001**
Inability due to unpaid labor	171	843	164	472	0.262	203	661	132	797	0.185
Total productivity costs	1,678	4,546	1,068	3,132	0.780	2,752	5,414	135	797	**<0.001**
Societal costs	3,465	5,487	2,759	4,016	0.432	4,449	6,184	1,946	2,950	0.073
Utilities	0.92	0.12	0.82	0.16	**<0.001**	0.90	0.14	0.86	0.15	0.860

SD, standard deviation

Table 3. Frequency of reported problems by dimension

EQ-5D Dimension		
Mobility	No problems	129 (80.1%)
	Slight problems	12 (7.5%)
	Moderate problems	18 (11.2%)
	Severe problems	1 (0.6%)
	Unable to	1 (0.6%)
	Total	161
Self-Care	No problems	155 (96.3%)
	Slight problems	3 (1.9%)
	Moderate problems	2 (1.2%)
	Severe problems	0
	Unable to	1 (0.6%)
	Total	161
Usual Activity	No problems	122 (75.8%)
	Slight problems	23 (14.3%)
	Moderate problems	11 (6.8%)
	Severe problems	2 (1.2%)
	Unable to	3 (1.9%)
	Total	161
Pain/Discomfort	No pain	101 (62.7%)
	Slight pain	39 (24.2%)
	Moderate pain	18 (11.2%)
	Severe pain	3 (1.9%)
	Unable to	0
	Total	161
Anxiety/Depression	No anxiety	128 (79.5%)
	Slight slight anxiety	26 (16.1%)
	Moderate anxiety	4 (2.5%)
	Severe anxiety	2 (1.2%)
	Unable to	1 (0.6%)
	Total	161

2.5. DISCUSSION

CRC represents a high economic burden in the Netherlands. In 2011, in the Netherlands, costs of CRC were about 488 million euros, that is 0.5% of the total healthcare costs and nearly 87% of these total costs were attributed to hospital costs.[22] In this study, the mean societal cost per CRC patient was estimated at €3,211 in the 3 months prior to surgery. The productivity losses represent a major part of these costs at 45.4% of total costs.

In the UK, Hall et al estimated costs of cancer care with the healthcare perspective that showed mean 15-month cumulative healthcare costs for CRC at £12,643 (approximately €15,945) per patient and concluded that <65 age group incurred greater costs than the >65 years age group which is in line with our study.[23] The study also demonstrated that the majority of the costs occurred within the first 6 months from diagnosis suggesting high costs during the primary treatment phase. Extracting the costs for the 3-month period from this study (15,945/15*3) results in €3,189, very similar to the 3-month societal costs in our study. An Asian study estimated direct medical costs at 24.81%, direct non-medical care costs at 38.04% and indirect costs at 37.14% of the total cost.[24] In this study, direct medical costs (healthcare costs) comprised of 54.5% and indirect costs (productivity costs) accounted for 45.4% of the total costs.

In another Finnish study by Niilo Farkkila, which estimates the costs CRC at different states of the disease, primary treatment (0–6 months after diagnosis) and advanced treatment states had the highest reported costs.[25] The cost for the 6-month interval between diagnosis and treatment (primary treatment period) was €22,200 which included direct healthcare costs, informal care costs and productivity losses. Productivity losses caused by CRC was substantial at €5,098 at the primary treatment state.[25] The overall costs vary depending on the number of years spent with CRC and degree of severity. It is therefore difficult to directly compare our study with this study and other previous studies due to various reasons. First, our study assessed the costs of patients for the period of 3 months and did not include the operative and postoperative costs which are considered to be the main cost drivers. Previous studies estimated total costs annually or longer than 12 months including surgery. Second, variations in valuation methodology such as using the human capital approach in previous studies and friction cost method in this study could affect the total costs. Higher productivity costs were estimated in Farkilla that used the human capital approach.

In our study, the quality of life scores was relatively high (0.88) and higher than the previous studies.[14, 26] Comparison to utility values in other studies should however be interpreted with caution as different tariffs for EQ-5D-5L have been used. To our knowledge, no study is available with utility value of the general Dutch population. Further comparison with the general Dutch population would be worthwhile. A study by Farkkila estimating the health-related quality of life in CRC showed a utility value of 0.760 in the primary treatment group (0–6 months after diagnosis).[14] Similarly, another study evaluating nationwide health utility showed a score of 0.67 in the acute period (<1 year) after a colon cancer diagnosis.[26] The high utility scores in our study could potentially be explained by the fact that our estimation was conducted just before surgery and that patients have a current better quality of life because of the surgery surveyance. Measurement of quality of life scores could also be biased or confounded due to the setting (hospital) or feelings of anxiety/excitement prior to surgery. The significant higher utility scores by men in our study could be explained by the fact that women usually self-report worse health than men.[27, 28] It is however difficult to assess if the differences in utility values are clinically meaningful which is beyond the scope of this study and further research would be required to investigate this.

This study has several limitations. First, costs and quality were estimated only at one time point. Baseline questionnaires were filled out on median preoperative day 1 (range preoperative day 8 to postoperative day 11). The recall period for the iMCQ and iPCQ were 3 months and 4 weeks respectively and iPCQ was extrapolated to 3 months. Second, we used a self-reported questionnaire which is known to cause recall bias. Third, we did not estimate transportation fees and out of pocket expenses which may have led to an under-estimation of the total costs. Lastly, we recruited the patients from the clinical trial which may limit the generalizability of the results. Limited use of exclusion criteria was used in an attempt to increase the generalizability of results.

Considering the fact that the median duration from the time of diagnosis to initiation of treatment for CRC in the Netherlands is 21 median days,[29] this paper provides an understanding of the initial costs of patients with CRC. The study reveals the importance of healthcare costs and productivity losses received by cancer patients. Earlier detection and improved treatments will hopefully lead to improved survival and reduced additional costs.

In conclusion, this study reveals that CRC costs impose substantial economic costs in the Netherlands. This study provides important information for future economic analyses and comparison of new interventions in patients with CRC. We recommend further research with larger sample and repeated cost and quality of life measurements to explore the change over time and the effects of surgery.

2.6. EXPERT OPINION

The economic burden of colorectal cancer is high. Important economic elements include healthcare costs and productivity losses among patients and caregivers. To date there is however, a scarcity of economic data and a large heterogeneity across studies is observed limiting comparisons. We recommend standardization of reporting and costing methods and development of data collection resources that improve the comparability of studies over time. In addition, to tackle colorectal cancer efficiently, we recommend to conduct cost-effectiveness analyses. Data from this article could serve as reference.

REFERENCES:

1. cancer Iafrf. fact_sheets_colorectalcancer 2017 [Available from: http://globocan.iarc.fr/old/FactSheets/cancers/colorectal-new.asp.
2. Bray F, Ferlay J, Laversanne M, Brewster DH, Gombe Mbalawa C, Kohler B, et al. Cancer Incidence in Five Continents: Inclusion criteria, highlights from Volume X and the global status of cancer registration. International journal of cancer. 2015;137(9):2060-71.
3. kankerregistratie N. 2017 [Available from: www.cijfersoverkanker.nl.
4. Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016;66(4):271-89.
5. Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet. 2014;383(9927):1490-502.
6. Schneider EC, Malin JL, Kahn KL, Ko CY, Adams J, Epstein AM. Surviving colorectal cancer : patient-reported symptoms 4 years after diagnosis. Cancer. 2007;110(9):2075-82.
7. Soerjomataram I, Thong MS, Ezzati M, Lamont EB, Nusselder WJ, van de Poll-Franse LV. Most colorectal cancer survivors live a large proportion of their remaining life in good health. Cancer Causes Control. 2012;23(9):1421-8.
8. Dunn J, Ng SK, Breitbart W, Aitken J, Youl P, Baade PD, et al. Health-related quality of life and life satisfaction in colorectal cancer survivors: trajectories of adjustment. Health Qual Life Outcomes. 2013;11:46.
9. Ramsey SD, Berry K, Moinpour C, Giedzinska A, Andersen MR. Quality of life in long term survivors of colorectal cancer. Am J Gastroenterol. 2002;97(5):1228-34.
10. Chambers SK, Meng X, Youl P, Aitken J, Dunn J, Baade P. A five-year prospective study of quality of life after colorectal cancer. Qual Life Res. 2012;21(9):1551-64.
11. Corral J, Castells X, Molins E, Chiarello P, Borras JM, Cots F. Long-term costs of colorectal cancer treatment in Spain. BMC Health Serv Res. 2016;16:56.
12. Volksgezondheidenzorg.info. 2017 [Available from: https://www.volksgezondheidenzorg.info/onderwerp/dikkedarmkanker/kosten/kosten#node-kosten-van-zorg-voor-dikkedarmkanker.
13. Segel JE. Cost-of-illness studies—a primer. RTI-UNC Center of Excellence in Health Promotion Economics. 2006:1-39.
14. Farkkila N, Sintonen H, Saarto T, Jarvinen H, Hanninen J, Taari K, et al. Health-related quality of life in colorectal cancer. Colorectal Dis. 2013;15(5):e215-22.
15. Larg A, Moss JR. Cost-of-illness studies: a guide to critical evaluation. Pharmacoeconomics. 2011;29(8):653-71.
16. Peters EG, Smeets BJJ, Nors J, Back CM, Funder JA, Sommer T, et al. Perioperative lipid-enriched enteral nutrition versus standard care in patients undergoing elective colorectal surgery (SANICS II): a multicentre, double-blind, randomised controlled trial. The lancet Gastroenterology & hepatology. 2018;3(4):242-51.
17. Peters EG, Smeets BJ, Dekkers M, Buise MD, de Jonge WJ, Slooter GD, et al. The effects of stimulation of the autonomic nervous system via perioperative nutrition on postoperative ileus and anastomotic leakage following colorectal surgery (SANICS II trial): a study protocol for a double-blind randomized controlled trial. Trials. 2015;16:20.

18. Kanters TA, Bouwmans CA, van der Linden N, Tan SS, Hakkaart-van Roijen L. Update of the Dutch manual for costing studies in health care. PloS one. 2017;12(11):e0187477.
19. Bouwmans C, Krol M, Brouwer W, Severens JL, Koopmanschap MA, Hakkaart L. IMTA Productivity Cost Questionnaire (IPCQ). Value Health. 2014;17(7):A550.
20. Hakkaart-van Roijen L, Van der Linden N, Bouwmans C, Kanters T, Tan SS. Kostenhandleiding. Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg In opdracht van Zorginstituut Nederland Geactualiseerde versie. 2015.
21. Versteegh MM, Vermeulen KM, Evers SM, de Wit GA, Prenger R, Stolk EA. Dutch tariff for the five-level version of EQ-5D. Value in health. 2016;19(4):343-52.
22. Volksgezondheidenzorg.info. https://www.volksgezondheidenzorg.info/onderwerp/dikkedarmkanker/kosten/kosten#node-kosten-van-zorg-voor-dikkedarmkanker [
23. Hall PS, Hamilton P, Hulme CT, Meads DM, Jones H, Newsham A, et al. Costs of cancer care for use in economic evaluation: a UK analysis of patient-level routine health system data. Br J Cancer. 2015;112(5):948-56.
24. Byun JY, Yoon SJ, Oh IH, Kim YA, Seo HY, Lee YH. Economic burden of colorectal cancer in Korea. J Prev Med Public Health. 2014;47(2):84-93.
25. Farkkila N, Torvinen S, Sintonen H, Saarto T, Jarvinen H, Hanninen J, et al. Costs of colorectal cancer in different states of the disease. Acta Oncol. 2015;54(4):454-62.
26. Ko CY, Maggard M, Livingston EH. Evaluating health utility in patients with melanoma, breast cancer, colon cancer, and lung cancer: a nationwide, population-based assessment. J Surg Res. 2003;114(1):1-5.
27. Cherepanov D, Palta M, Fryback DG, Robert SA. Gender differences in health-related quality-of-life are partly explained by sociodemographic and socioeconomic variation between adult men and women in the US: evidence from four US nationally representative data sets. Qual Life Res. 2010;19(8):1115-24.
28. Jorngarden A, Wettergen L, von Essen L. Measuring health-related quality of life in adolescents and young adults: Swedish normative data for the SF-36 and the HADS, and the influence of age, gender, and method of administration. Health Qual Life Outcomes. 2006;4:91.
29. Helsper CCW, van Erp NNF, Peeters P, de Wit NNJ. Time to diagnosis and treatment for cancer patients in the Netherlands: Room for improvement? European journal of cancer (Oxford, England : 1990). 2017;87:113-21.

CHAPTER 3

The clinical and economic impact of postoperative ileus in patients undergoing colorectal surgery

Published as:
Peters EG, Pattamatta M, Smeets BJJ, Brinkman DJ, Evers SMAA, de Jonge WJ, Hiligsmann M, Luyer MDP. The clinical and economical impact of postoperative ileus in patients undergoing colorectal surgery. Neurogastroenterology & Motility. 2020 Aug;32(8):e13862 doi: 10.1111/nmo.13862.

ABSTRACT

Background: Colorectal surgery is associated with postoperative ileus (POI). Despite its widespread manifestation, the influence of POI on recovery, quality of life (QoL), and costs is largely unknown. The aim of this study was to assess whether the inflammatory processes found in experimental studies are also evident in patients undergoing colorectal surgery. In addition, the impact of POI on short and long-term QoL and costs was investigated.

Methods: We analyzed the outcomes of the SANICS-II trial, including prospective evaluation of inflammatory parameters in blood samples, costs from a societal perspective and QoL, using validated questionnaires. Outcomes were compared between patients with and without POI, and in particular patients with POI as unique complication.

Key Results: A total of 265 patients (POI, n=66 vs non-POI, n=199) were included and 38/66 had POI as only complication. CRP levels were significantly increased on postoperative day (POD)1, 2, 3 and 4 in patients with POI. Furthermore, plasma levels of cytokines IL-6, Il-8 and IL-10 were significantly increased the first two days after resection. Patients with POI had a higher overall complication rate and a reduced QoL 3 months postoperatively, even in the only-POI group. Moreover, mean societal cost per patient with POI were 38-47% higher at 3 months postoperatively.

Conclusions & Inferences: Supporting findings from experimental studies, inflammatory parameters were increased in patients with only POI and comparable with all patients with POI. These results demonstrate the impact and large contribution of POI in postoperative inflammation, costs and QoL in patients undergoing colorectal surgery.

KEY POINTS

- Postoperative ileus (POI) is a common complication in patients, however translation of experimentally found mechanisms and resolutions to the clinical setting remain challenging.
- This study found that patients with POI had a higher inflammatory response, more complications, an increased length of stay, a decreased quality of life and more healthcare costs.
- This study confirms the association of POI with inflammation and demonstrates the burden of POI on patients, the healthcare system and society.

3.1. INTRODUCTION

Colorectal surgery is associated with a substantial complication rate. In particular, postoperative ileus (POI) is affecting 10 - 40% of patients undergoing a colorectal resection and is an important clinical determinant of short-term morbidity.[1] POI is often seen as an inevitable complication of abdominal surgery, and attempts have been made to reduce the incidence by Enhanced Recovery After Surgery protocols, less opioid use and studies investigating the use of chewing gum.[2] Still, POI is leading to discomfort, impaired recovery, a prolonged length of hospital stay, reoperation and readmission.[3, 4] Notably, an association exists between POI and anastomotic leakage, further indicating the impact of POI on postoperative morbidity.[5]

Complications after colorectal surgery have impact on the quality of life (QoL) and are associated with a substantial increase in costs.[6, 7] However, it is unknown what the significance of POI is in these costs and quality of life, in the short and long term after patients have been discharged. Furthermore, clinically relevant therapeutic strategies for POI are lacking, although the underlying mechanism of POI has been unraveled in rodent models.[8] Such models point out that POI is triggered by local inflammatory infiltrates and is associated with systemic inflammatory markers. Manipulation of the intestine induces activation of macrophages, mast cells and enteric glial cells.[9-11] Vagus nerve stimulation has been shown in experimental models to be effective in reducing the inflammatory process underlying POI.[12] Also, stimulation of the vagus nerve via lipid-enriched nutrition, was effective in several experimental models, although such an effect of lipid-enriched nutrition was not observed in a large double-blind randomized controlled trial (SANICS II trial).[13] However, despite the insight into molecular cues to POI development, little progress is made in translating these experimental findings to a clinical practice. The reason for this discrepancy between the experimental data and the implementation into clinical practice may be twofold; on the one hand there is a lack of consensus amongst physicians towards the clinical features of POI, its impact, and its management, resulting in few high quality clinical studies also in a surgical setting.[14] On the other hand, it is uncertain whether the mechanisms found in rodent models can be completely translated into the clinical setting.[15-18] The aim of the current study is to address whether inflammatory processes such as those found in experimental studies, occur in patients undergoing colorectal surgery. In addition, the impact of POI on short and long-term QoL and costs was investigated.

3.2. MATERIALS AND METHODS

This is a sub-study from a previous international multicenter double-blind randomized controlled trial (SANICS II trial) in three Dutch hospitals and three Danish hospitals.[13] The trial was designed to compare lipid-rich nutrition administrated just before, during and after colorectal resection to standard care (no nutrition). The original study was approved by the Medical Ethics Committee of the Catharina Hospital (Eindhoven, The Netherlands) and was reported according to the CONSORT guidelines. The principles of Good Clinical Practice and the Declaration of Helsinki were followed. The trial was registered with ClinicalTrials.gov (number NCT02175979) and trialregister.nl (number NTR4670). Further details regarding the trial design and outcomes have previously been reported.[13, 19]

3.2.1. Population and setting

In the SANICS II trial described earlier, 280 patients were randomized, 15 of whom were excluded after random allocation because they fulfilled one or more exclusion criteria. All 265 patients analyzed in the original trial were considered for inclusion in the current study. Briefly, inclusion criteria were age 18 years or older and undergoing elective segmental colorectal resection with primary anastomosis. The exclusion criteria were a previous gastric or esophageal resection, peritoneal metastases, a pre-existing or the creation of an ileostomy, and the use of glucocorticosteroids or medication that disrupted acetylcholine metabolism (e.g., selective serotonin reuptake inhibitors or anticonvulsants). All patients provided written informed consent. Patients were randomly assigned to the intervention or control group and stratification was applied to ensure an equal distribution between colonic and rectal surgery and between laparoscopic and open procedures. In the present study, patients were stratified into two groups including those with and without POI. First, in order to assess the true influence of POI, an analysis was performed in a selected group of patients in which patients with POI as unique complication (n=38/66) were compared with patients that did not develop any complications after surgery (n=144/199). Second, the total study population (n=265) was analyzed to investigate the contribution of POI to other complications, inflammation, QoL and costs.

3.2.2. Clinical outcomes

POI is the primary outcome in the original trial and is measured clinically. POI was scored by the definition as described by Vather et al.[20] Patients had to meet the following criteria at postoperative day (POD) 4 after colorectal surgery: lack of flatus or stool passage and inability to tolerate a regular oral diet. We also included late POI which is established when the symptoms of POI (lack of flatus or stool passage and inability to tolerate an oral diet) are first experienced after POD 4. Patients were instructed to register presence of nausea or vomiting, passage of flatus and defecation, and consumption of a regular oral diet in a diary daily. All surgical complications within 30 days postoperatively were registered and graded according to the Clavien–Dindo Classification of Surgical Complications.[21] Secondary outcomes included length of stay, readmissions, health-related QoL and costs and the inflammatory response.

3.2.3. Measurement of the inflammatory response

Blood samples were collected from all patients at four predefined time points. Samples were taken the day before surgery and 4, 24 and 48 hours after onset of surgery. All the blood samples were immediately put on ice, centrifuged at 4ºC and 3000 g for 12 minutes and the plasma was stored at −80°C until further analysis. To determine the most important inflammatory cytokines, a Human Inflammatory Cytokines Kit was used to measure cytokine levels of IL-1β, IL-6, IL-10, IL-8, IL12p70 and TNF-α by cytometric bead array (BD Biosciences, Erenbodengem, Belgium) according to manufacturer's instructions. CRP (C-reactive protein) measurement was part of the standardized care and the outcomes were retrieved from the medical chart. As such, CRP was only measured postoperatively, on postoperative day (POD) 1, 2, 3 and 4. CRP levels were determined by an immunoturbodimetric assay (Roche/Hitachi cobas c system, Roche, Rotkreuz, Switzerland).

Data on costs and QoL were collected by means of questionnaires for the period between August 2014 and August 2017, at three time points namely preoperatively, at 3 months and at 6 months postoperatively. Patients who completed the questionnaires at least at two time points were included for this analysis.

3.2.4. Costs

The Institute for Medical Technology Assessment (iMTA) Medical consumption questionnaire (iMCQ) was used to measure the healthcare costs; these include hospitalizations, medical procedures, medications, outpatient clinic visits etc. The iMTA productivity cost questionnaire (iPCQ) was used to measure the costs due to productivity losses in two domains 1) paid work due to absenteeism and presentism and 2) unpaid work.[22] The costs were expressed and analyzed in Euros. The updated Dutch manual for Costing Analysis in Healthcare Research was used for valuation of the healthcare costs.[23] Costs were divided into three categories: 1) healthcare sector costs; 2) costs for patient and family; and 3) productivity costs. Healthcare costs consisted of medication costs, consultations with healthcare professionals, use of diagnostic methods and the frequency of inpatient stay and outpatient treatment. The identified health services consumed by the patient were multiplied with their corresponding unit prices. Total costs were estimated by summing the individual services. Medication costs were based on the price per dosage of the drug in the Netherlands. Patient and family costs included the use of formal (paid care) and informal care (unpaid care). The costs for unpaid care were valued using the proxy good method, which values the time spent on informal care at the labor market price of a close market substitute. Productivity costs included productivity losses due to absence from work and were valued using friction cost method. The friction cost method which takes into account production losses confined to the period needed to replace the sick employee (85 days).[23]

3.2.5. Quality of life and utilities

QoL was assessed using the five level, five dimensional EQ-5D-5L, which is a standardized measure of health status developed by the Euroqol group. EQ-5D-5L consists of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension was scored on a five-point scale which represented 'no problems', 'slight problems', 'moderate problems', 'severe problems', and 'extreme problems'. Utilities were derived from EQ-5D-5L using Dutch tariffs.[24] The five dimensions can be summed into a health state. Utility values can be calculated for these health states, using preferences elicited from a general population, the so called Dutch algorithm. Here, utility is used to measure a single value between 0 and 1, that reflects the health-related quality of life of the patient.

In colorectal cancer patients, QoL was further assessed using the European Organization for the Research and Treatment of Cancer Quality of life Questionnaire Cancer Core-30 (EORTC QLQ C-30). The scale ranges from 0 to 100, with higher scores indicating higher level of functioning for Global Quality of Life, Physical, Role, Emotional, Cognitive and Social Functioning and Fatigue. For financial problems higher scores indicate increased difficulty.

3.3. STATISTICAL METHODS

All statistical data were analyzed using SPSS V.25 (IBM, Armonk, NY, USA). Graphics were conducted with GraphPad Prism version 7 (GraphPad Software, La Jolla, CA, USA) Cost data are presented as means with 95% confidence interval and unpaired t-test was used to compare the cost means.[25] To compare continuous data between groups, the data were tested for normal distribution (with skewness and kurtosis). Consequently, the Mann–Whitney U test was used for utility and inflammatory parameters, and the data were presented as medians. Analyses of inflammatory parameters were predefined in the protocol and chosen according to literature.[11, 15, 26] Inflammatory parameters were treated as independent samples, CRP and cytokine measurements were compared per time point for the chosen conditions and no multiple comparisons have been applied. Univariate logistic regression was used to identify risk factors on POI. A multivariable logistic regression model was developed using factors identified as significant in univariate analyses as well as clinically relevant factors, including the following variables: American Society of Anesthesiologists (ASA) grade, colon or rectal surgery, open or laparoscopic surgical approach, duration of surgery, intraoperative blood loss and opioid use postoperatively. A two-tailed P value < 0.05 was considered significant.

3.4. RESULTS

A total of 265 patients were included in this study. Patients with only POI (n=38) were compared to patients without developing any complication (n=144). Furthermore, 66 patients in total met the criteria of POI, and 199 patients did not have POI. In the group of patients with only POI, 17/38 were operated laparoscopically (45%), and in the group without complications laparoscopic surgery was performed in 95/144 patients (66%). Demographics and clinical characteristics are outlined in Table 1

Multivariate logistic regression analysis showed that ASA-III grade (OR 4.08 CI 0.64-6.80 $P = 0.002$), smoking (OR 4.13 CI 1.40-11.84 $P = 0.008$) and duration of surgery in minutes (OR 1.01 CI 1.00-1.02 $P = 0.018$) were associated with POI. To evaluate the systemic inflammatory response to surgery, CRP was routinely measured postoperatively and was significantly increased on postoperative day (POD) 1, POD2, POD3 and POD4 in patients with only POI compared to patients without complications ($P = 0.016$, $P < 0.001$, $P = 0.001$, $P = 0.047$ respectively) (Figure 1A). On predefined time points for every patient plasma cytokine measurements were performed. As expected, preoperative cytokine levels were not different in patients with or without POI. Four hours after start of surgery, a trend towards higher IL-6 for patients with only POI was shown ($P = 0.054$). Moreover, at 24 - 48 hours after surgery, cytokine levels showed an increase in patients with POI as only complication. The most pronounced difference between only-POI and patients without complications was shown in IL-6 levels (24 h: $P = 0.027$; 48 h: $P = 0.016$). Furthermore, patients who only developed POI as complication had elevated levels of IL-8 at 24 h ($P = 0.047$) and 48 h ($P = 0.015$) compared to patients without complications. Also, levels of IL-10 were significantly elevated in patients with only POI compared to no complications at 48 h: $P = 0.012$ (Figure 1B-D). IL-1β, TNF-a and IL-12p70 were not different between groups, however concentrations in most samples were below detection limit (Figure 1E-G).

Results of the analysis of the total study population, including patients that had other complications as well, were comparable with the results of the only POI and no complications groups. CRP was significantly increased on POD 2, 3 and 4 in patients with POI compared to patients without POI (POD2: $P < 0.001$; POD3: $P < 0.001$; POD4: $P = 0.003$) (Figure 2A). Subsequently, levels of IL-6 (24 h: $P = 0.017$ and at 48 hr: $P = 0.003$), IL-8 (48 h: $P = 0.001$) and IL-10 (24 h: $P = 0.036$ and 48 hr: $P = 0.003$) were elevated significantly in patients who developed POI compared to patients without POI (Figure 2B-G). A summary of the inflammatory markers is shown in Table S1 supplementary data.

Table 1. Demographic characteristics

	No complications (N=144)	only POI (N=38)	P- value
Age (years)	67 [63-72]	67 [61-76]	0.839
Male	84 (58)	21 (55)	0.733
Female	60 (42)	17 (45)	
Body Mass Index (kg/m²)	25.3 [22.3-27.7]	26.7 [23.7-30.0]	0.159
ASA grade			0.005
I	34 (24)	4 (11)	
II	98 (68)	24 (63)	
III	12 (8)	10 (26)	
Smoking	13 (9)	9 (24)	0.023
Alcohol	115 (78)	21 (55)	0.002
Diabetes Mellitus	14 (10)	6 (16)	0.379
Previous abdominal surgery	46 (32)	18 (47)	0.077
Malignancy	135 (94)	35 (92)	0.716
Neo-adjuvant treatment	18 (13)	8 (21)	0.18
Surgical approach			
Laparoscopic	95 (66)	17 (45)	0.017
Open	49 (34)	21 (55)	
Type of resection			0.138
Colon	118 (82)	27 (71)	
Rectum	26 (28)	11 (29)	
Deviating colostomy	19 (13)	12 (32)	0.007
Duration of surgery (min)	140 [118-170]	168 [120-225]	0.02
Intraoperative blood loss (mL)	100 [40-200]	150 [100-325]	<0.001
Perioperative nutrition (intervention)	72 (50)	19 (50)	1,000
Opioid use postoperatively	119 (83)	36 (95)	0.062

The data are n (%) or the median [interquartile range]. ASA = American Society of Anesthesiologists.

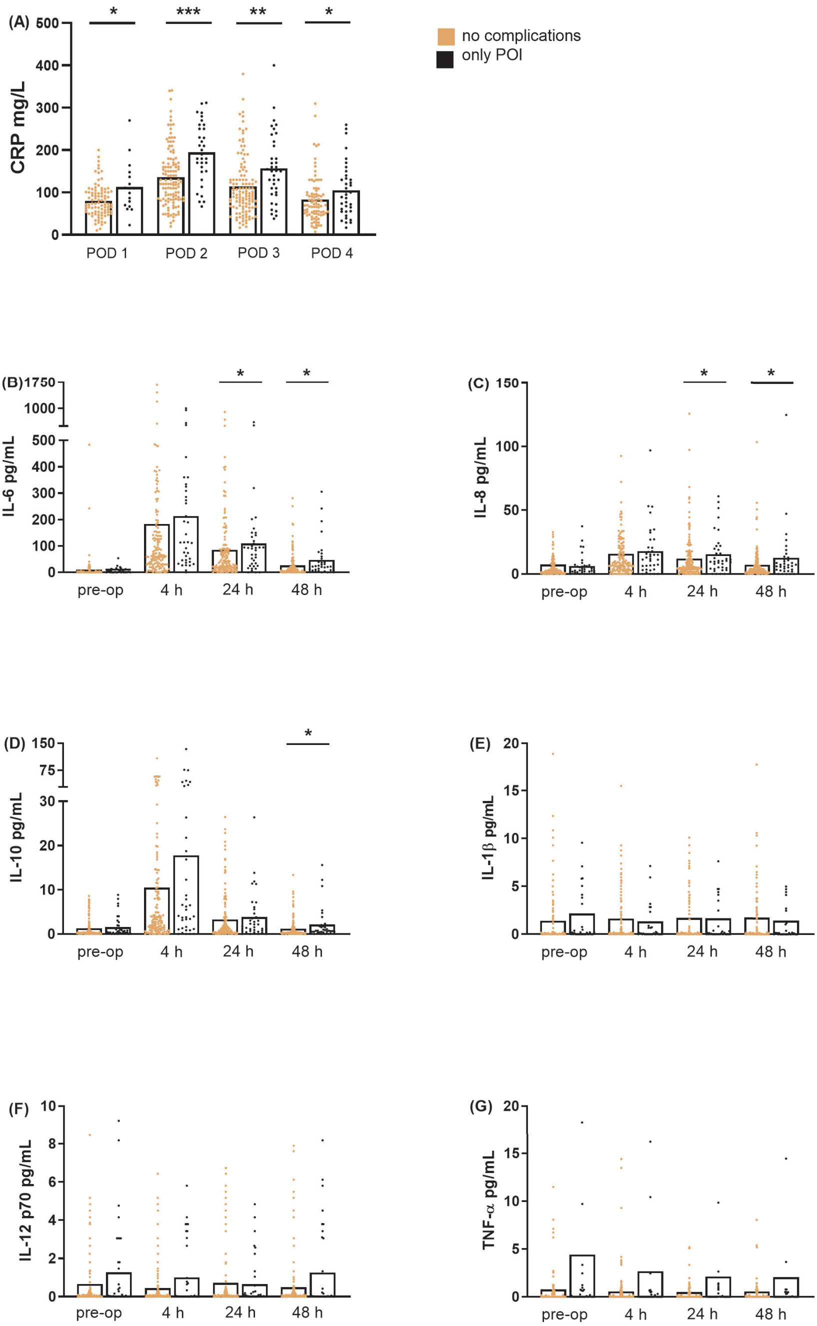


Figure 1. Analysis showing perioperative circulating CRP and cytokine levels in patients with only post-operative ileus (POI) (n=38) against patients without complications (n=144). Every single dot represents a patient, the bar indicates the mean. CRP was significantly elevated on postoperative day (POD) 1, 2, 3 and 4 in patients with only POI. IL-6 and IL-8 showed a significant increase 24 hours and 48 hours after surgery, IL-10 after 48 hours (Mann-Whitney U test). *P < 0.05, ** P < 0.01, and *** P < 0.001.

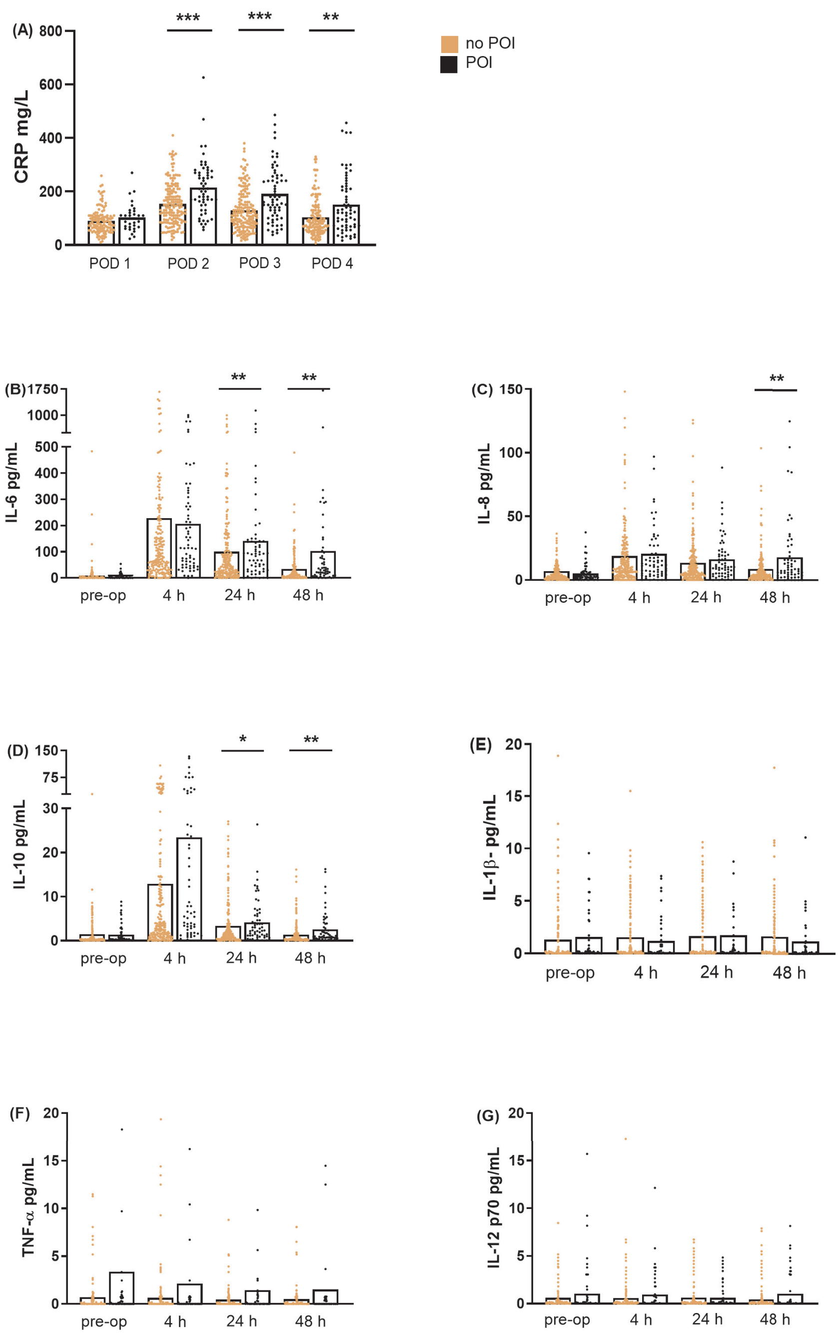


Figure 2. Perioperative circulating CRP and cytokine levels in patients with (n=66) and without postoperative ileus (POI) (n=199), every single dot represents a patient, the bar indicates the mean. CRP was significantly elevated on postoperative day (POD) 2, 3 and 4 in patients with POI. IL-6 and IL-10 showed a significant increase 24 hours and 48 hours after surgery, IL-8 after 48 hours (Mann-Whitney U test). *P < 0.05, ** P < 0.01, and *** P < 0.001.

3.4.1. Costs and QoL assessments

In total 259/265 (98%) patients completed the questionnaires at baseline, 85% (224/265) of the questionnaires were completed postoperatively at 3 months and 82% (216/265) at 6 months postoperatively. Thirty-two patients with missing questionnaires at two time points were excluded from the analysis. This resulted in a total of 233 (88%) patients to be included in the analysis, of which 53 patients were reported with POI and 180 patients without POI. Of these, 32 patients had POI as only complication and 133 had an uncomplicated recovery. Furthermore 15 patients with a non-malignant disease were excluded from the EORTC analysis.

3.4.2. Costs

Costs were calculated from a societal perspective meaning that all the monetary benefits were included regardless of who pays the costs and who gain the benefits. At 3 months postoperatively, mean societal cost per patient was 38% higher for patients with POI as the only postoperative complication compared to patients without complications (€10647 vs €6606; $P = 0.022$; Table 2). Moreover, analyses of all patients with POI showed 47% higher mean societal costs than for all patients without POI (€14529 vs €7702; $P < 0.001$; Table 2).

3.4.3. Quality of life

Median utility score was significantly lower three months postoperatively in patients with only POI (0.85 IQR 0.76 – 0.98), compared to patients without complications (0.89 IQR 0.83 - 1; $P = 0.023$). This effect was even more remarkable in all patients with POI at 3 months, who scored significantly lower on health-related QoL than patients without POI (utility score 0.85 IQR 0.75 - 0.91 vs 0.89 IQR 0.81 - 1; $P = 0.002$). This difference was also apparent at 6 months postoperatively; the utility score in patients with POI was 0.84 IQR 0.75 - 0.92 compared to 0.89 IQR 0.82 - 1 in those without POI ($P = 0.017$; Table 2).

Table 2. Costs and utilities in patients undergoing colorectal surgery

	Selection of patients					**All patients**				
	No complications (N=133)		POI only (N=32)		P- value	No POI (N=180)		POI (N=53)		P- value
Cost (€)										
Baseline	4274 (1401)	2986-5562	6537 (2963)	2951-10123	0.154	5052 (1457)	3752-6354	7549 (3290)	4605-10494	0.087
3 Months	6606 (4595)	5200-8013	10647 (7228)	6605-14689	0.022	7702 (5631)	6458-8946	14529 (10968)	10246-18813	<0.001
6 Months	3353 (1354)	2469-4238	3240 (2161)	1798-4683	0.908	3765 (1497)	2910-4620	3856 (2456)	2407-5305	0.919
Utility										
Baseline	0.91	0.88-1	0.89	0.81-1	0.035	0.91	0.88-1	0.89	0.81-1	0.031
3 Months	0.89	0.83-1	0.85	0.76- 0.98	0.023	0.89	0.81-1	0.85	0.75- 0.91	0.002
6 Months	0.89	0.84-1	0.85	0.80-0.92	0.083	0.89	0.82-1	0.84	0.75-0.92	0.017

Costs and utility over a period of three months. Cost values are Mean (Median) and 95% CI. Utility values are Median and IQR.

Table 3. Complications

	No POI (n=199)	POI (n=66)	P-value
Any complication (besides POI)	55 (28%)	28 (42%)	0.025
Number of complications besides POI			0.002
0	144 (72%)	38 (58%)	
1	44 (22%)	13 (20%)	
2	9 (6%)	10 (15%)	
3	1 (0.5%)	3 (5%)	
4	1 (0.5%)	1 (1.5%)	
6	0	1 (1.5%)	
Reoperations	11 (8%)	13 (20%)	0.001
Length of stay (median; days)	5 [4-6]	11 [8-15]	<0.001
Readmissions (within 30 days)	13 (9%)	11 (17%)	0.013

The data are n (%) or the median [interquartile range].

Considering the EQ-5D-5L health profile levels (no problems = level 1 and problems = levels 2 to 5) patients with POI as only complication were more likely to experience at least some problems relative to patients without complications. This effect was mostly shown in the dimensions mobility, usual activity and pain. Patients with only POI experienced more mobility problems (47%) than patients without complications (27%) at 3 months and even more at 6 months (66% vs 32%). The same was shown in usual activity: at 3 months 66% of patients with only POI vs 37% of patients without complications experienced problems and at 6 months 56% vs 38% experienced problems in usual activity, respectively. Pain did still impact QoL at 3 months in 63% (only POI) vs 48% (no complications). Accordingly, in the total analysis, half of the patients with a period of POI experienced problems in mobility at 3 months (49% POI vs 32% no POI) and at 6 months this increased until 60% in POI patients and 36% in patients without POI. This trend was also shown in problems in usual activity: 68% (POI) versus 43% (no POI) at 3 months, and at 6 months 60% (POI) versus 43% (no POI). Pain did still impact QoL at 3 months in 66% of all the patients with POI, while in 49% of patients without POI. (Table S2 supplementary data)

The EORTC-QLQ-C30 indicates the level of functioning in patients. At 3 months, patients with POI as only complication had significantly lower scores in Physical functioning and Role functioning than patients without complications. At 6 months, patients with only POI still had lower scores on Physical functioning (Figure 3). When other complications were included, patients with POI had lower scores on Global quality of life, Physical functioning, and Role functioning at 3 months, and still experienced lower scores on Global quality of life and Role functioning, and also in Emotional functioning at 6 months, compared to patients without POI (Figure 3).

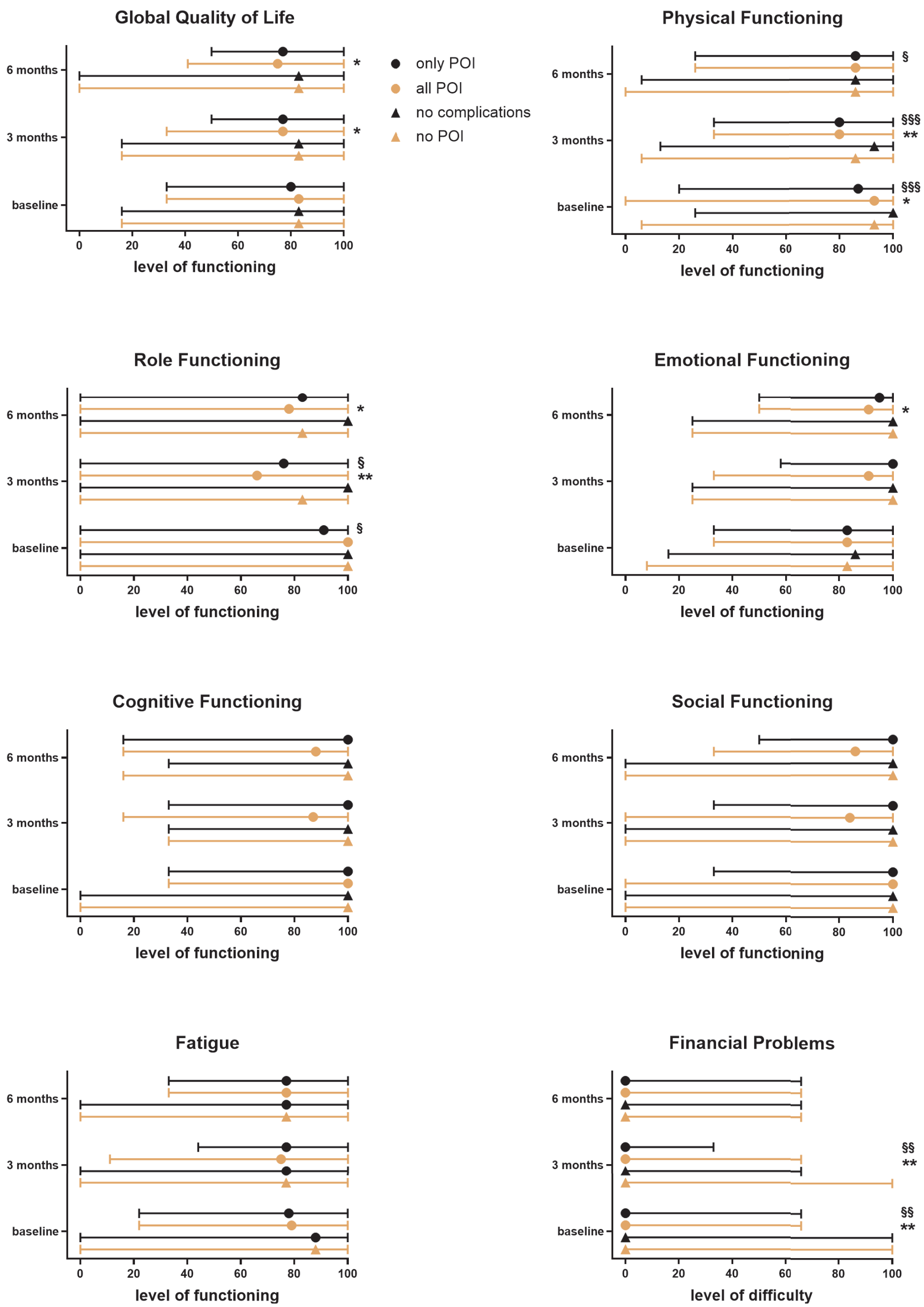


Figure 3. EORTC-QLQ-C30 level of functioning in categories measured at baseline, three months and six months after surgery in patients with POI as unique complication versus patients with no complications and all POI versus non-POI patients. Higher scores indicate higher levels of functioning except for financial difficulties. Data are medians (dots) and ranges. § P<0.05, §§ P<0.01 and §§§ P<0.001 for only POI (●) vs no complications (▲). *P<0.005 and **P<0.01 for all POI (●) vs no POI (▲).

3.4.4. Complications, length of stay and readmission

The observation of elevated inflammatory biomarkers in patients suffering from POI, was also associated with a higher complication rate. Patients with POI experienced more complications than patients without POI; 42% (28/66) of the patients with POI had one or more accompanying complications, compared to 28% (55/199) of the patients without POI that had a complication ($P = 0.025$). Multivariate logistic regression analysis showed that ASA-III grade (OR 4.53 CI 1.61-12.75 $P = 0.004$) and duration of surgery in minutes (OR 1.01 CI 1.00-1.01 $P < 0.001$) were associated with POI in the total study population. Corrected for ASA-grade, smoking and duration of surgery, patients with POI remained at risk to have one or more accompanying complications (OR 2.31 CI 1.25-4.27 $P = 0.007$). In addition, POI patients had a significantly higher number of complications (Table 3) and more severe complications, graded by the Clavien-Dindo classification: 17% (11/66) of the patients with POI had a Clavien-Dindo grade 3b or higher complication versus 8% (15/199) of patients without POI ($P = 0.031$). This means that patients with POI experienced another complication more often, either for which an intervention under general anesthesia was required, or leading to ICU admission or to death. In more detail, 14/66 POI patients also developed anastomotic leakage, against 9/199 of non-POI patients ($P < 0.001$), and 9 vs 4 patients developed pneumonia, respectively ($P = 0.001$). No change was found in the rate of wound infection (4 vs 11 patients; $P = 1.00$). Length of stay, readmissions within 30 days of discharge and reoperations were all significantly increased in patients with POI (Table 3). Length of stay was significantly associated with POI when corrected for other complications, ASA-grade, rectal surgery and duration of surgery (OR 1.51 CI 1.34-1.70 $P < 0.001$). In addition, patients with POI as only complication were on average admitted 4 days longer than patients with an uncomplicated recovery. The length of stay of patients without complications was median 4 days (IQR 3 - 6 days) and was for only-POI patients median 8 days (IQR 7 - 12 days, $P < 0.001$). Furthermore, 5% (2/38) of patients with only POI underwent additional surgical laparoscopy because of clinical deterioration with no new findings, and 13% (5/38) of only POI patients was readmitted to the hospital within 30 days after discharge.

3.4.5. Laparoscopic and open surgery

It is recognized that the surgical approach, open or laparoscopic surgery, has effect on surgical outcomes. In this study, both open and laparoscopic cases were included. Therefore, additional analyses were performed on the total study population. In patients undergoing open surgery 30% (34/112) developed POI. In the group undergoing laparoscopic procedure 21% (32/153) developed POI ($P = 0.079$). Length of stay was 6 days longer in the POI group compared to the non-POI group, and when stratified for open and laparoscopic approach, patients were admitted 5 days longer when they received open surgery and developed POI (6 days IQR 5 - 7 no POI; vs 11 days IQR 8 – 15 POI) and 4 days longer when patients had laparoscopic surgery and developed POI (4 days IQR 3 - 5 no POI; vs 8 days IQR 7 – 12 POI).

There was no difference in open or laparoscopic surgery in patients with POI and other complications, i.e. patients who had an open procedure and had POI did not develop more complications than laparoscopic operated patients.

In addition, patients without complications were admitted 1 day longer when they received open surgery compared to laparoscopic surgery (5 days IQR 5 - 7 open surgery; vs 4 days IQR 3 - 5 laparoscopic surgery). Moreover, patients were also admitted 1 day longer when they had POI as only complication and had open surgery than laparoscopic surgery (9 days IQR 8 - 14 open surgery; vs 8 days IQR 7 - 12 laparoscopic surgery).

Next, there was a clear difference in level of inflammation between patients that had laparoscopic surgery and open surgery. Inflammation was significantly lower in patients that had a laparoscopic procedure 4 hours, 24 hours and 48 hours after surgery for IL-6, IL-8 and IL-10. Of note, this significant difference was already apparent before surgery (0 hours). For CRP inflammation was only lower on POD1 for laparoscopic surgery compared to open surgery (Table S3 supplementary data). Interestingly, as demonstrated earlier, while IL-6 levels are significantly higher in patients with only POI compared to patients without complications 24 and 48 hours after surgery and similar higher levels of IL-6 in laparoscopic versus open surgery, in case of stratifying the POI patients and the patients without complications for laparoscopic and open surgery, results are not significant. For Il-6, between laparoscopic and open surgery, levels increase. CRP levels are more consistent; levels of CRP do not differ much between open or laparoscopic surgery, and significant higher levels of CRP remain in POI patients compared to no complications.

3.5. DISCUSSION

We report here that patients having colorectal surgery resulting in POI as a complication, had a higher level of circulating inflammatory biomarkers, an increased length of stay, a decreased quality of life and more healthcare costs compared to patients with uncomplicated recovery. This study provides novel information because data was analyzed in patients with POI as a unique complication, where most studies allow for a mix of postoperative events possibly leading to bias. Moreover, these results were consistent in the total study population in which patients with other complications were included. Patients with POI were more at risk to develop other and more severe complications. The results of this study regarding the rise of inflammatory markers are in agreement with those of animal studies showing that increased levels of inflammatory cytokines and chemokines are detectable systemically next to a localized inflammation in the gut following its manipulation during surgery.[5, 27, 28] Furthermore, we demonstrate that POI is a strong driving factor in upregulating the inflammatory response after surgery, irrespective of the surgical open or laparoscopic approach.

Recently, a study of Boersema et al[26] showed an association between systemic cytokines and postoperative complications in patients, and IL-6, also elevated in our study, had the best diagnostic value in predicting infectious complications. Of note, patients with POI had higher levels of IL-6 and CRP in that study, however not significantly because of a small sample size. We observed elevated levels of IL-10 in our study as well, and those were similarly reported by others to occur in the early phase of POI in patients, being significantly increased in patients with longer recovery from POI in abdominal surgery.[29] Remarkably, in animal models IL-1β has been suggested to play an important role in POI pathology,[10] however systemic levels of IL-1β were very low and no differences were shown between patients with and without POI, which was also reported by Boersema and colleagues.[26]

Another important finding in this study is the confirmation of data from experimental studies that inflammation is elevated early after manipulation of the intestine. An increased inflammatory response early after surgery may be causal for development of POI.[11] The analysis of patients with POI as only complication showing increased inflammation supports this, as soon as 24 hours after onset of surgery CRP and IL-6 have risen significantly. Besides, in the total study population, co-existing complications could also contribute, many of these complications present later in the postoperative period. For instance, the interval between surgery and anastomotic leakage was median 7 days in patients with POI that developed anastomotic leakage in this study, which is in line with earlier studies where a median interval of 6-12 days was reported for anastomotic leakage and 8 days for all infectious complications.[30-33] Importantly, POI is associated with anastomotic leakage, although the causal relation of anastomotic leakage and POI is to be determined.[5] Irrespective, reducing early inflammatory activation could be considered to reduce both POI and anastomotic leakage in patients at risk. From another point of view, higher cytokine levels, regardless of its cause, indicate poorer outcomes: Patients develop POI and are at significant risk of developing other adverse outcomes. This was shown in this study with POI patients having another complication in 42%, while non-POI patients developed a complication in 28%, with an odds ratio of 2.31. Therefore, POI may be an early marker of complications or maybe even a marker of poor outcomes in the setting of other complications.

In animal studies, interventions have been explored aiming to reduce the early inflammatory responses that lie at the basis of POI. For instance, prucalopride, a5-Ht4 receptor agonist, and vagus nerve stimulation, either electrical or via lipid-enriched nutrition inhibits inflammation in an early stage and can prevent experimental POI.[18, 34, 35] Interestingly, two recent clinical pilot studies by Stakenborg et al showed promising results in patients. Preoperative administration of prucolapride resulted in decreased local IL-6 and IL-8 expression and improved clinical recovery in a small cohort of patients.[18 36] In another pilot study in which abdominal vagus nerve stimulation was investigated in patients that underwent colorectal surgery was shown that nerve stimulation could reduce levels of cytokines induced by *ex vivo* lipopolysaccharide (LPS) stimulation of whole blood. This suggests a systemic modulatory effect on immune cells, and there is great potential for future studies in this field. However, it remains uncertain whether the interventions that were effective in animal studies have an effect on POI clinically, especially since enteral nutrition was not able to reduce POI in a clinical trial performed by our group.[13]

Many different risk factors for POI have been described.[37-39] In this study ASA grade and duration of surgery were independent risk factors. It is notable that patients with POI as only complication did smoke and used alcohol more often. Furthermore, these patients had more open surgery, more intraoperative blood loss and received a colostomy more often. Of note, some of the patients that reported lower levels of QoL preoperatively, in particularly physical functioning, developed POI as only complication. Patients with POI experienced reduced QoL in different modalities. This effect was not limited to the direct postoperative period, but remained evident three and six months after surgery, emphasizing the long-term impact of the burden of POI in patients. The current results are in line with a prospective study where the impact of postoperative complications after colorectal cancer surgery on long-term QoL was investigated,[6] though specific selection of patients with POI had not yet been applied. Besides, POI was associated with additional complications, which evidently affects the QoL of these patients. In the present study, QoL was still reduced after three months in the selected group of patients with POI as unique complication. This is remarkable, and shows that POI which usually resolves in a couple of days in the hospital and is often considered a minor complication has great impact on patients' lives, even months after discharge. It is likely that in the total population anastomotic leakage and pneumonia contribute to an increased length of stay and costs, and a reduced QoL in patients with POI even 6 months after surgery. Since patients with POI are at significant risk of developing other complications, POI leaves its mark on society. Furthermore, an earlier study showed a relationship between POI and other complications and a higher mortality rate in patients with POI and additional complications.[4] The latter is one of the few studies that analyzed POI as unique complication, however only reports on 30 day-mortality for the POI only group, which was equal to patients without POI (1%). In the past, few studies have calculated costs for patients with POI, and some did not report if patients had other complications as well. A retrospective cohort study of Iyer et al in the United States showed a mean difference of $8000 for patients with POI vs without POI in hospitalization costs.[3] Another retrospective study of Asgeirsson et al[40] of 184 patients that underwent a colectomy showed similar results (US $16612 vs $8316), obtaining their cost data through a hospital accounting system. In a more recent study, POI patients were found to be more expensive even after adjustment for major complications and length of stay.[41] In the current study data were prospectively collected and all the relevant costs from the broadest perspective were included in an economic evaluation, thereby measuring the impact on society.[23] Interestingly, data on complications in colorectal surgery showed that 31% of the total hospital costs were spent on complications.[7] Conversely, we show that patients with POI have a higher chance of developing other complications which is accompanied with a 9% rise in costs and decline in Global QoL. The data from our study emphasize the societal impact (both QoL and costs) of POI and the necessity to keep searching for applicable therapeutics and reduce costs.[42]

The strengths of this study are that data were prospectively collected as part of a RCT with a clear definition of POI as primary outcome, a high response rate regarding cost and QoL data and almost complete data on inflammatory markers. Analyses were done on both a selected group of patients that only developed POI, as well as the whole study population, representing the general population undergoing colorectal surgery to substantiate the results. This study has also limitations. First, systemic cytokine levels were determined, whereas cytokine levels locally in the bowel wall may be a better reflection of a local inflammatory response associated with POI. Second, costs and QoL were assessed by self-reported questionnaires which may result in recall bias, although the overall completion rate was 88%. The cost elements for all participating centers (of which some are located in Denmark) reflect the reference prices from the Netherlands which may have influenced the total cost estimates.

In conclusion, POI has a significant negative impact on quality of life, increases length of stay and is associated with a higher overall complication rate. The differences between the selected group of patients with POI as unique complication (n=38) and the total group of patients with POI who developed other complications as well (n=66) are relatively small, demonstrating the impact of POI and the large contribution of POI in postoperative inflammation, length of stay, costs and QoL in the general population of patients undergoing colorectal surgery. This study confirms the association of POI with inflammation and this supports that therapeutic strategies need to be developed aimed at reducing the inflammatory response to reduce the burden of POI following colorectal surgery.

REFERENCES

1. van den Heijkant TC, Costes LM, van der Lee DG, Aerts B, Osinga-de Jong M, Rutten HR, et al. Randomized clinical trial of the effect of gum chewing on postoperative ileus and inflammation in colorectal surgery. Br J Surg. 2015;102(3):202-11.
2. Peters EG, De Jonge WJ, Smeets BJ, Luyer MD. The contribution of mast cells to postoperative ileus in experimental and clinical studies. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society. 2015;27(6):743-9.
3. Iyer S, Saunders WB, Stemkowski S. Economic burden of postoperative ileus associated with colectomy in the United States. Journal of managed care pharmacy : JMCP. 2009;15(6):485-94.
4. Tevis SE, Carchman EH, Foley EF, Harms BA, Heise CP, Kennedy GD. Postoperative Ileus--More than Just Prolonged Length of Stay? Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2015;19(9):1684-90.
5. Peters EG, Dekkers M, van Leeuwen-Hilbers FW, Daams F, Hulsewe KW, de Jonge WJ, et al. Relation between postoperative ileus and anastomotic leakage after colorectal resection: a post hoc analysis of a prospective randomized controlled trial. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2016.
6. Brown SR, Mathew R, Keding A, Marshall HC, Brown JM, Jayne DG. The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. Annals of surgery. 2014;259(5):916-23.
7. Govaert JA, Fiocco M, van Dijk WA, Scheffer AC, de Graaf EJ, Tollenaar RA, et al. Costs of complications after colorectal cancer surgery in the Netherlands: Building the business case for hospitals. Eur J Surg Oncol. 2015;41(8):1059-67.
8. Bragg D, El-Sharkawy AM, Psaltis E, Maxwell-Armstrong CA, Lobo DN. Postoperative ileus: Recent developments in pathophysiology and management. Clin Nutr. 2015;34(3):367-76.
9. Kalff JC, Schraut WH, Simmons RL, Bauer AJ. Surgical manipulation of the gut elicits an intestinal muscularis inflammatory response resulting in postsurgical ileus. Annals of surgery. 1998;228(5):652-63.
10. Stoffels B, Hupa KJ, Snoek SA, van Bree S, Stein K, Schwandt T, et al. Postoperative ileus involves interleukin-1 receptor signaling in enteric glia. Gastroenterology. 2014;146(1):176-87 e1.
11. Boeckxstaens GE, de Jonge WJ. Neuroimmune mechanisms in postoperative ileus. Gut. 2009;58(9):1300-11.
12. de Jonge WJ, van der Zanden EP, The FO, Bijlsma MF, van Westerloo DJ, Bennink RJ, et al. Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. Nature immunology. 2005;6(8):844-51.
13. Peters EG, Smeets BJJ, Nors J, Back CM, Funder JA, Sommer T, et al. Perioperative lipid-enriched enteral nutrition versus standard care in patients undergoing elective colorectal surgery (SANICS II): a multicentre, double-blind, randomised controlled trial. The lancet Gastroenterology & hepatology. 2018;3(4):242-51.
14. Kehlet H, Williamson R, Buchler MW, Beart RW. A survey of perceptions and attitudes among European surgeons towards the clinical impact and management of postoperative ileus. Colorectal disease : the official journal of the Association of Coloproctology of Great Britain and Ireland. 2005;7(3):245-50.

15. The FO, Bennink RJ, Ankum WM, Buist MR, Busch OR, Gouma DJ, et al. Intestinal handling-induced mast cell activation and inflammation in human postoperative ileus. Gut. 2008;57(1):33-40.
16. Chapman SJ, Pericleous A, Downey C, Jayne DG. Postoperative ileus following major colorectal surgery. The British journal of surgery. 2018;105(7):797-810.
17. Vilz TO, Roessel L, Chang J, Pantelis D, Schwandt T, Koscielny A, et al. Establishing a biomarker for postoperative ileus in humans - Results of the BiPOI trial. Life Sci. 2015;143:58-64.
18. Stakenborg N, Labeeuw E, Gomez-Pinilla PJ, De Schepper S, Aerts R, Goverse G, et al. Preoperative administration of the 5-HT4 receptor agonist prucalopride reduces intestinal inflammation and shortens postoperative ileus via cholinergic enteric neurons. Gut. 2018.
19. Peters EG, Smeets BJ, Dekkers M, Buise MD, de Jonge WJ, Slooter GD, et al. The effects of stimulation of the autonomic nervous system via perioperative nutrition on postoperative ileus and anastomotic leakage following colorectal surgery (SANICS II trial): a study protocol for a double-blind randomized controlled trial. Trials. 2015;16:20.
20. Vather R, Trivedi S, Bissett I. Defining postoperative ileus: results of a systematic review and global survey. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2013;17(5):962-72.
21. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of surgery. 2004;240(2):205-13.
22. Bouwmans C, Krol M, Severens H, Koopmanschap M, Brouwer W, Hakkaart-van Roijen L. The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. Value Health. 2015;18(6):753-8.
23. Kanters TA, Bouwmans CAM, van der Linden N, Tan SS, Hakkaart-van Roijen L. Update of the Dutch manual for costing studies in health care. PLoS One. 2017;12(11):e0187477.
24. M MV, K MV, S MAAE, de Wit GA, Prenger R, E AS. Dutch Tariff for the Five-Level Version of EQ-5D. Value Health. 2016;19(4):343-52.
25. Mani K, Lundkvist J, Holmberg L, Wanhainen A. Challenges in analysis and interpretation of cost data in vascular surgery. Journal of vascular surgery. 2010;51(1):148-54.
26. Boersema GSA, Wu Z, Menon AG, Kleinrensink GJ, Jeekel J, Lange JF. Systemic Inflammatory Cytokines Predict the Infectious Complications but Not Prolonged Postoperative Ileus after Colorectal Surgery. Mediators of inflammation. 2018;2018:7141342.
27. van Bree SH, Cailotto C, Di Giovangiulio M, Jansen E, van der Vliet J, Costes L, et al. Systemic inflammation with enhanced brain activation contributes to more severe delay in postoperative ileus. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society. 2013;25(8):e540-9.
28. Wehner S, Schwarz NT, Hundsdoerfer R, Hierholzer C, Tweardy DJ, Billiar TR, et al. Induction of IL-6 within the rodent intestinal muscularis after intestinal surgical stress. Surgery. 2005;137(4):436-46.
29. Stein K, Lysson M, Schumak B, Vilz T, Specht S, Heesemann J, et al. Leukocyte-Derived Interleukin-10 Aggravates Postoperative Ileus. Front Immunol. 2018;9:2599.
30. Komen N, Dijk JW, Lalmahomed Z, Klop K, Hop W, Kleinrensink GJ, et al. After-hours colorectal surgery: a risk factor for anastomotic leakage. Int J Colorectal Dis. 2009;24(7):789-95.

31. Hyman N, Manchester TL, Osler T, Burns B, Cataldo PA. Anastomotic leaks after intestinal anastomosis: it's later than you think. Annals of surgery. 2007;245(2):254-8.
32. Welsch T, Muller SA, Ulrich A, Kischlat A, Hinz U, Kienle P, et al. C-reactive protein as early predictor for infectious postoperative complications in rectal surgery. Int J Colorectal Dis. 2007;22(12):1499-507.
33. Singh PP, Zeng IS, Srinivasa S, Lemanu DP, Connolly AB, Hill AG. Systematic review and meta-analysis of use of serum C-reactive protein levels to predict anastomotic leak after colorectal surgery. The British journal of surgery. 2014;101(4):339-46.
34. Lubbers T, Buurman W, Luyer M. Controlling postoperative ileus by vagal activation. World journal of gastroenterology : WJG. 2010;16(14):1683-7.
35. Hong GS, Zillekens A, Schneiker B, Pantelis D, de Jonge WJ, Schaefer N, et al. Non-invasive transcutaneous auricular vagus nerve stimulation prevents postoperative ileus and endotoxemia in mice. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society. 2019;31(3):e13501.
36. Stakenborg N, Wolthuis AM, Gomez-Pinilla PJ, Farro G, Di Giovangiulio M, Bosmans G, et al. Abdominal vagus nerve stimulation as a new therapeutic approach to prevent postoperative ileus. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society. 2017.
37. Kronberg U, Kiran RP, Soliman MS, Hammel JP, Galway U, Coffey JC, et al. A characterization of factors determining postoperative ileus after laparoscopic colectomy enables the generation of a novel predictive score. Annals of surgery. 2011;253(1):78-81.
38. Chapuis PH, Bokey L, Keshava A, Rickard MJ, Stewart P, Young CJ, et al. Risk factors for prolonged ileus after resection of colorectal cancer: an observational study of 2400 consecutive patients. Annals of surgery. 2013;257(5):909-15.
39. Vather R, Bissett IP. Risk factors for the development of prolonged post-operative ileus following elective colorectal surgery. Int J Colorectal Dis. 2013;28(10):1385-91.
40. Asgeirsson T, El-Badawi KI, Mahmood A, Barletta J, Luchtefeld M, Senagore AJ. Postoperative ileus: it costs more than you expect. J Am Coll Surg. 2010;210(2):228-31.
41. Mao H, Milne TGE, O'Grady G, Vather R, Edlin R, Bissett I. Prolonged Postoperative Ileus Significantly Increases the Cost of Inpatient Stay for Patients Undergoing Elective Colorectal Surgery: Results of a Multivariate Analysis of Prospective Data at a Single Institution. Diseases of the colon and rectum. 2018.
42. Vonlanthen R, Slankamenac K, Breitenstein S, Puhan MA, Muller MK, Hahnloser D, et al. The impact of complications on costs of major surgical procedures: a cost analysis of 1200 patients. Annals of surgery. 2011;254(6):907-13.

SUPPLEMENTARY INFORMATION

Table S1. Inflammatory markers in patients with POI compared to patients without complications

		Selection of patients			All patients		
		No complications (n=144)	POI only (N=38)	P- value	No POI (N=199)	POI (N=66)	P- value
CRP	POD 1	73 [54-101]	110 [69-142]	0.016	82 [56-110]	99 [67-125]	0.140
	POD 2	122 [84-170]	190 [149-255]	<0.001	143 [93-203]	210 [150-270]	<0.001
	POD 3	97 [67-140]	150 [98-215]	0.001	110 [74-172]	169 [110-259]	<0.001
	POD 4	70 [48-97]	95 [56-137]	0.047	82 [55-130]	120 [70-216]	0.003
IL-6	0 h	1.0 [0.2-3.8]	2.0 [0.3-8.3]	0.303	1.3 [0.3-4.3]	1.6 [0.4-6.3]	0.477
	4 h	65.2 [30.2-170.2]	113.8 [42.8-316.7]	0.054	82.8 [32.4-198.2]	114.6 [47.3-282.8]	0.059
	24 h	35.9 [14.4-87.5]	90.1 [24.8-137.7]	0.027	44 [17.7-110.5]	91.4 [29.5-142.3]	0.017
	48 h	9.7 [2.4-24.5]	21.9 [7.1-51.9]	0.016	12.1 [2.8-43.1]	27.4 [8.5-87.1]	0.003
IL-8	0 h	2.6 [1.1-6.9]	2.8 [1.4-6.8]	0.543	2.9 [1.3-6.7]	2.7 [1.3-5.8]	0.609
	4 h	8.0 [3.4-20.3]	12.9 [4.9-23.9]	0.172	9.1 [3.8-22.0]	11.7 [4.6-27.1]	0.346
	24 h	5.2 [2.9-14.4]	10.2 [4.5-20.9]	0.047	6.9 [3.6-17.1]	10.3 [5.0-22.0]	0.052
	48 h	3.3 [1.4-7.7]	7.0 [2.8-13.0]	0.015	3.9 [1.7-9.4]	7.7 [3.3-19.6]	0.001
IL-10	0 h	0.3 [0.1-1.0]	0.5 [0.2-1.9]	0.204	0.3 [0.1-1.1]	0.4 [0.2-1.2]	0.480
	4 h	2.8 [1.0-9.6]	5.5 [1.2-24.1]	0.087	3.3 [1.1-11.5]	5.3 [1.3-25.5]	0.106
	24 h	1.1 [0.4-3.3]	1.7 [0.7-5.1]	0.149	1.3 [0.5-3.6]	2.3 [0.9-5.8]	0.036
	48 h	0.4 [0.2-1.2]	0.7 [0.4-1.8]	0.012	0.5 [0.2-1.4]	0.9 [0.5-3.3]	0.003

C-reactive protein (mg/L) and cytokines (in pg/mL) measured on predefined moments perioperatively. Values are median and [IQR].

Table S2. Percentage of reported problems by dimension and complication group

	Baseline %		3 months %		6 months %	
EQ-5D dimension	No POI	POI	No POI	POI	No POI	POI
Mobility problems						
selection	11	34	27	47	32	66
all	14	32	32	49	36	60
Self-care problems						
selection	2	9	4	6	4	9
all	2	10	9	9	7	8
Usual Activity problems						
selection	19	31	37	66	38	56
all	20	32	43	68	43	60
Pain/Discomfort						
selection	30	50	48	63	53	47
all	33	47	49	66	54	58
Anxiety/Depression						
selection	19	16	14	9	15	13
all	19	21	16	19	16	21

Numbers are percentages. Selected group of patients (selection): n=165, with POI only n=32 and no complications n=133. Total study population (all): n=233, with POI n=53 and no POI n=180.

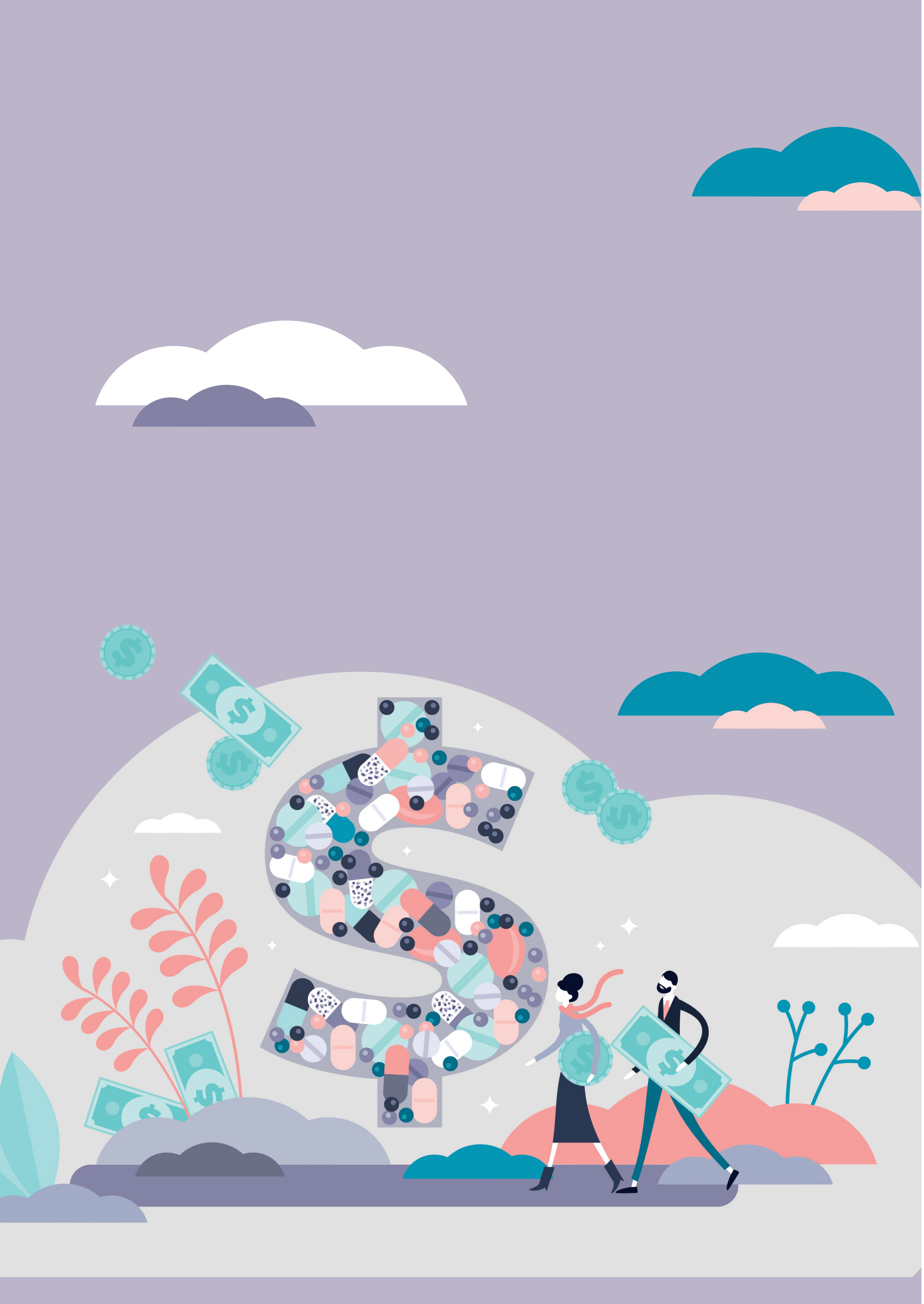
Table S3. Inflammatory markers in patients that received laparoscopic surgery compared to open surgery

Parameter		Laparoscopic surgery (N=153)	Open surgery (N=112)	P- value
CRP	POD 1	75 [51-102]	101 [71-139]	<0.001
	POD 2	155 [93-211]	169 [117-233]	0.098
	POD 3	129 [80-190]	130 [85-220]	0.319
	POD 4	90 [56-170]	91 [60-150]	0.788
IL-6	0 h	1.0 [0.2-3.5]	1.7 [0.5-8.7]	0.038
	4 h	62.3 [31.4-150-7]	151.2 [62-360]	<0.001
	24 h	36.1 [14.3-107]	77.9 [30.8-150.2]	0.001
	48 h	11.0 [2.7-43.6]	23 [6.0-61.1]	0.003
IL-8	0 h	2.3 [1.1-4.7]	4.1 [2.2-8.7]	<0.001
	4 h	7.3 [3.4-14.9]	15.9 [6.6-32.7]	<0.001
	24 h	5.3 [2.9-13.3]	11.3 [5.3-22.7]	<0.001
	48 h	3.4 [1.6-8.0]	7.0 [3.4-15.7]	<0.001
IL-10	0 h	0. [0.1-0.8]	0.4 [0.2-2.1]	0.029
	4 h	2.5 [0.8-8.2]	6.6 [1.8-28.7]	<0.001
	24 h	1.2 [0.4-3.3]	2.0 [0.8-5.3]	0.006
	48 h	0.5 [0.2-1.2]	0.8 [0.4-2.3]	0.001

C-reactive protein (mg/L) and cytokines (in pg/mL) measured on predefined moments perioperatively. Values are median and [IQR].

PART II

Economic evaluations



CHAPTER 4

Health-related quality of life and cost-effectiveness analysis of gum chewing in patients undergoing colorectal surgery: results of a randomized controlled trial

Published as:
Pattamatta M, Smeets BJJ, Evers SMAA, Rutten HJT, Luyer MDP, Hiligsmann M. Health-related quality of life and cost-effectiveness analysis of gum chewing in patients undergoing colorectal surgery: results of a randomized controlled trial. Acta Chirurgica Belgica. 2018 Oct;118(5):299-306. doi: 10.1080/00015458.2018.1432742.

ABSTRACT

Background: Postoperative ileus (POI) and anastomotic leakage (AL) following colorectal surgery severely increase healthcare costs and decrease quality of life. This study evaluates the effects of reducing POI and AL via perioperative gum chewing compared to placebo (control) on in-hospital costs, health-related quality of life (HRQoL), and assesses cost-effectiveness.

Methods: In patients undergoing elective, open colorectal surgery, changes in HRQoL were assessed using EORTC-QLQ-C30 questionnaires and costs were estimated from a hospital perspective. Incremental cost-effectiveness ratios were estimated.

Results: In 112 patients, mean costs for ward stay were significantly lower in the gum chewing group when compared to control (€3522 (95% CI €3034-€4010) versus €4893 (95% CI €3843-€5942), respectively, p = 0.020). No differences were observed in mean overall in-hospital costs, or in mean change in any of the HRQoL scores or utilities. Gum chewing was dominant (less costly and more effective) compared to the control in more than 50% of the simulations for both POI and AL.

Conclusion: Reducing POI and AL via gum chewing reduced costs for ward stay, but did not affect overall in-hospital costs, HRQoL, or mapped utilities. More studies with adequate sample sizes using validated questionnaires at standardized time points are needed.

4.1. INTRODUCTION

Postoperative outcomes following colorectal surgery have markedly improved since the implementation of fast-track protocols [1]. However, the incidence of severe complications including anastomotic leakage (AL) (up to 19%) and postoperative ileus (POI) (up to 45%) remains substantial [1-4]. Postoperative complications strongly increase healthcare costs and negatively impact both short and long term quality of life (QoL) [5-12].

In a recent randomized trial, perioperative gum chewing significantly reduced POI (14/52 patients versus 29/60 patients) and AL (2/52 patients versus 8/60 patients) when compared to placebo [4]. However, given the current trend of rising healthcare expenditures, new interventions cannot be implemented in routine care based on clinical efficacy alone. Economic evaluations are warranted to determine the value for money of an intervention [13]. While perioperative gum chewing had a clear beneficial effect on clinical outcomes [4], the effects on in-hospital costs and QoL are unknown.

This study evaluates the effects of reducing POI and AL via perioperative gum chewing compared to control on in-hospital costs and health-related quality of life (HRQoL), and estimates cost-effectiveness in patients undergoing colorectal cancer surgery.

4.2. MATERIALS AND METHODS

This is a substudy from a previous multicenter, single-blind, randomized controlled trial in two large Dutch tertiary referral hospitals (Catharina Hospital and Orbis Medical Center) [4]. The original trial was conducted according to the Declaration of Helsinki, and was approved by the local Medical Ethics Committee on November 19th, 2008 (No 08-T-70). All patients signed informed consent prior to participation.

4.2.1. Patient population

Patients were included in the original trial as described elsewhere [4]. Briefly, patients were eligible for inclusion if aged 18 or older and undergoing elective, open colorectal surgery. Patients were excluded in case of the presence of peritoneal carcinomatosis, inflammatory bowel disease, a history of gastric or esophageal surgery, a disturbance of acetylcholine metabolism owing to neurological disease or depression, pre-existing ileostoma, allergy to mint, or if using agents influencing gut motility (including opioids) or acetylcholine metabolism.

4.2.2. Interventions

Patients were randomly allocated to the intervention or placebo group. Patients in the intervention group started chewing gum at least three hours prior to the start of surgery, and again three hours after end of surgery. Patients in the control group received a placebo dermal patch three hours before the start of surgery and were instructed to not chew gum. Both the intervention and control were discontinued when patients started an oral diet [4]. Further details on the intervention and control are described in the original trial report [4].

4.2.3. Clinical outcomes

The primary outcome of the original study was length of stay. Secondary outcome measures included POI and AL [14].

4.2.4. Health-related quality of life and utilities

Health-related quality of life was a secondary endpoint in the original trial [4] and was assessed preoperatively and postoperatively using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30 version 3.0) [15]. The time point for completion of the postoperative QLQ-C30 questionnaire was not standardized. Missing data were imputed according to the EORTC guidelines [15].

Utilities are preference weights for different health states in which more preferred health states receive more weight. Utility scores range between 0 (death) and 1 (perfect health). Mapping was done to compute utility scores from HRQoL-scores [16]. The differences between the pre- and post-operative HRQoL and utility scores were reported as changes in mean.

4.2.5. Costs

Costs were calculated from the hospital perspective. In-hospital costs were determined by retrospectively extracting financial data from the electronic patient registration system. Additionally, costs for readmission within 1 year after surgery due to complications stemming from the primary operation were included. Costs were estimated using a bottom-up approach. Only the standardized unit costs of the Catharina Hospital were available; consequently these were also used for units of care from the Orbis Medical Centre. Costs were categorized into fees for the primary operation, pathology, laboratory tests, radiological examinations, intramural consults, therapeutic interventions under local anesthesia, re-operations, and admission costs for staying in the surgical ward and/or intensive care unit. Monetary units are expressed in Euros (€) and were indexed for the year 2011, as this was the year in which most patients were included in the original trial [4]

4.2.6. Cost-effectiveness evaluation

The implementation of a new treatment depends on the maximum amount of money that society is willing to pay for a gain in effectiveness, which is termed the “threshold” or “ceiling-ratio”. The gain in effectiveness is most commonly expressed in quality-adjusted life years (QALYs) [17]. However, it was considered inappropriate to estimate QALYs from the available data, since the time point for postoperative QoL assessment was not standardized, and the required utility scores needed to be mapped from the EORTC QLQ-C30 scores. Instead, cost-effectiveness was assessed using the two clinical outcomes that were significantly reduced by perioperative gum chewing in the original trial (POI and AL) [4]. A cost-effectiveness analysis was performed by determining the incremental cost-effectiveness ratio (ICER) of gum chewing in comparison with the control. ICERs were calculated by dividing the incremental costs by the incremental effects; the sample uncertainty concerning the ICERs was quantified by conducting 5000 bootstrapping replications. The ICERs are presented on a cost-effectiveness plane, which is divided into four quadrants. When the intervention is more effective and less costly than the comparator, the ICERs lie in the southeast quadrant and the intervention is considered dominant. Conversely, when the intervention is less effective and more costly, the ICERs lie in the northwest quadrant and the intervention is considered inferior. When the intervention is more costly and yet more effective, the ICERs lie in the northeast quadrant and when intervention is less costly and less effective, the ICERs lie in the southwest quadrant. A treatment is cost-effective when it is dominant.

As there is uncertainty surrounding the threshold per avoided incident of POI or AL, cost-effectiveness acceptability curves (CEAC) were used to present the results of the bootstrapping. A CEAC is a graphic representation of the uncertainty in differences in cost and effect between the two groups, showing the probability of an intervention being cost-effective for a wide range of threshold values.

4.3. STATISTICAL ANALYSIS

Normally distributed data are presented as means (standard deviation) and were tested using the unpaired t-test, while non-parametric data are presented as median [range] and were tested using the Mann-Whitney U test. Categorical variables were tested with the X^2 test. Cost data are presented as means, medians and 95% confidence intervals, as is recommended for cost-analysis studies [18]. Cost means are compared using the unpaired t-test.

As perioperative gum chewing was hypothesized to affect only the postoperative course and not the type of operation and subsequent pathology analysis of the resected tissue, a sensitivity analysis was performed in which only postoperative costs were included.

Furthermore, as the original study was not powered to detect changes in HRQoL or costs, a post hoc power analysis was performed using an α equal to 0.05 to assess the statistical power of the current analysis. The statistical power (mean ± S.D.) of preoperative, postoperative, and delta change HRQOL scores were 0.29 ± 0.26, 0.12 ± 0.2 and 0.07 ± 0.06 respectively. The statistical power analysis for total costs, total admission costs and total readmission costs showed a power of 0.04, 0.05 and 0.05 respectively.

4.4. RESULTS

4.4.1. Patient characteristics

A total of 120 patients were included in the original study, of which 58 patients were randomized to the intervention group and 62 patients to the control group. Groups were similar at baseline with regard to demographic variables, co-morbidities, and operative details (Table 1, adapted with permission from Heijkant et al. [4]). Eight patients were excluded after randomization due to technical reasons[4] and were not included in any analysis in this paper.

Table 1. Baseline characteristics

	Gum Chewing (N=58)	Control (N=62)	P-value
Age (years)[a]	66 ± 9	67 ± 11	0.864*
Sex ratio(M:F)	38 : 20	46 : 16	0.300
Height (cm)[a]	173 ± 9	172 ± 9	0.906*
Weight(kg)[a]	80 ± 17	77 ± 11	0.267*
BMI(kg/m2)[a]	27 ± 5	26 ± 4	0.283*
ASA fitness grade			
I	8 (14)	10 (16)	
II	44 (76)	45 (73)	
III	6 (10)	7 (11)	
Previous abdominal surgery	14 (24)	17 (27)	0.820
Diabetes mellitus	10 (17)	11 (18)	0.898
Smoking	6 (10)	10 (16)	0.799
Alcohol use	18 (31)	24 (39)	0.258
SSRI use	1 (2)	1 (2)	0.925
Duration of surgery(min)[b]	135 [65-491]	142 [65-452]	0.584**
Blood loss[b]	300 [0-2000]	300 [0-4000]	0.896**
Colostomy required	29 (50)	29 (47)	0.855
Type of operation			1.000
Right hemicolectomy	16 (28)	17 (27)	
Left colectomy	18 (31)	20 (32)	
Rectal resection	22 (38)	23 (37)	
Other	2 (3)	2 (3)	

Values are presented as number (%) or as [a]mean(S.D) or [b]median [range]. All tests are $\chi 2$ test, except * unpaired t-test and ** Mann-Whitney U test. ASA, American society of Anesthesiologists; SSRI, selective serotonin reuptake inhibitor. Adapted with permission from Heijkant et al.

Table 2: Health-related quality of life and mapped utility scores in gum chewing versus control

	Preoperative (N = 96)			**Postoperative (N = 69)**			**Change (N = 66)**		
Dimension	Gum chewing	Control	P-value	Gum chewing	Control	P-value	Gum chewing	Control	P-value
Global quality of life	75 [0 - 100]	75 [0 - 100]	0.64	50 ± 22	51 ± 21	0.87	17 [-83 - 83]	15 [-41 - 58]	0.67
Physical functioning	93 [53 - 106]	93 [20 - 100]	0.11	66 [0 - 100]	46 [13 - 100]	0.71	30 ± 30	26 ± 26	0.58
Role functioning	100 [0 - 100]	83 [0 - 100]	0.07	29 ± 34	30 ± 29	0.94	50 [-16 - 100]	50 [-16 - 100]	0.33
Emotional functioning	91 [0 - 100]	75 [0 - 100]	**<0.01**	83 [16-100]	66 [8 - 100]	**0.02**	8 [-41 - 66]	8 [-91 - 75]	0.69
Cognitive functioning	100 [16 - 100]	100 [33 - 100]	0.3	83 [0 - 100]	83 [16 - 100]	0.47	16 [-33 - 100]	16 [-16 - 66]	0.89
Social functioning	100 [0 - 100]	100 [0 - 100]	0.51	75 [0 - 100]	66 [33 -95]	0.17	16 [-66 - 83]	16 [-50 - 100]	0.77
Fatigue	18 ± 18	29 ± 27	**0.03**	56 ± 25	59 ± 25	0.67	-40±27	-28±30	0.12
Nausea/vomiting	0 [0 - 16]	0 [0 - 66]	0.43	16[0 - 100]	33 [0 - 83]	0.6	-27 ± 34	-25 ± 25	0.73
Pain	0 [0 -16]	0 [0-66]	0.43	16 [0 - 100]	33 [0 - 83]	0.6	-29 ± 35	-25 ± 25	0.64
Dyspnea	0 [0 - 66]	0 [0 - 100]	0.87	25 ± 30	27 ± 27	0.74	0 [-100 - 0]	0 [-100 - 66]	0.74
Insomnia	0 [0 - 100]	33 [0 - 100]	0.13	33 [0 - 100]	33 [0 - 100]	0.39	-14 ± 37	-12 ± 30	0.74
Appetite loss	0 [0 -100]	0 [0 - 100]	**0.02**	33 [0 - 100]	33 [0 - 100]	0.28	-33 [-100 - 100]	-33 [-100 - 66]	0.53
Constipation	0 [0 - 100]	0 [0 - 100]	0.98	0 [0 - 100]	0 [0 - 100]	0.24	0 [-100 - 100]	0 [-66 - 33]	0.49
Diarrhea	0 [0 - 100]	0 [0 - 100]	0.75	0 [0 - 100]	0 [0 - 100]	0.61	0 [-66 - 100]	0 [-100 - 66]	0.48
Financial problems	0 [0 - 66]	0 [0 - 100]	0.62	0 [0 - 66]	0 [0 - 100]	0.1	0 [-33 - 0]	0 [-33 - 0]	0.31
Utilities	0.90 [0.27 - 0.98]	0.82 [-0.04 - 0.98]	**0.01**	0.61 ± 0.24	0.57 ± 0.21	0.43	0.26 [-0.33 - 0.81]	0.21 [-0.63 - 0.78]	0.53

Values are mean ± standard deviation or median [range]

4.4.2. Clinical outcomes

As noted in the original study report, incidence of POI was significantly lower in the gum chewing group compared to the control group (14/52 patients versus 29/60 patients, respectively, $p = 0.02$).[4] Furthermore, fewer patients in the gum chewing group experienced AL, in comparison with the control group (2/52 patients versus 8/60 patients, respectively, $p = 0.03$) [4].

4.4.3. Health-related quality of life and utilities

Out of 112 patients, 95 patients completed the preoperative baseline questionnaire and 69 patients completed the postoperative questionnaire. A total of 66 patients completed both the pre- and postoperative questionnaires. The time point of completing the postoperative questionnaire was similar in both groups: median postoperative day 6 (range 2-39) in the gum chewing group and median postoperative day 8 (range 2-70) in the control group ($p = 0.19$). On average, 0.31 out of 30 questions were imputed per questionnaire. Pre- and postoperative HRQoL and mapped utility scores, and the change in scores between the two time points, are summarized in Table 2. The pre- and postoperative emotional functioning scale showed a significantly higher mean score in the gum chewing group ($p < 0.01$ and $p = 0.02$, respectively). The preoperative fatigue scale showed a significantly lower score in the gum chewing group ($p = 0.03$). Preoperatively, patients in the control group had significantly more appetite loss in comparison with the patients in the gum chewing group ($p = 0.02$). No other significant differences were seen between groups.

At baseline, patients in the gum chewing group showed a higher score in utilities ($p = 0.01$); however postoperative utilities and change in utilities between the two time points were similar between groups ($p = 0.43$ and $p = 0.53$, respectively).

4.4.4. Costs

In-hospital costs are presented in Table 3. Total costs for admission ($p = 0.71$), total costs for readmission ($p = 0.78$), and total costs for admission and readmission combined ($p = 0.85$) were not statistically different between groups. However, mean costs for ward stay were lower in the gum chewing group when compared to the control group ($p = 0.02$). In the sensitivity analysis, which excluded costs for primary operation and pathology analysis, there were no differences in postoperative admission costs, or in the combined postoperative admission and readmission costs ($p = 0.67$ and $p = 0.82$, respectively).

Table 3. In-hospital costs

	Gum Chewing			Control			
	Mean	Median	95% CI	Mean	Median	95% CI	P-value
Total admission costs	11579	8322	7890 - 15268	12486	8628	9257 - 15715	0.711
Operative costs							
Primary operation	3034	2194	2556 - 3512	2924	2405	2529 - 3320	0.722
Pathology	148	71	101 - 195	154	71	94 - 215	0.875
Postoperative costs							
Laboratory	474	248	176 - 772	459	272	275 - 644	0.931
Radiology	133	38	59 - 208	152	38	72 - 231	0.740
Consultations	95	73	67 - 124	138	56	88 - 188	0.140
Therapeutic intervention	318	0	18 - 617	505	0	-65 - 1076	0.578
Re-operation	306	0	11 - 601	326	0	76 - 577	0.917
Ward stay	3522	3067	3034 - 4010	4893	3505	3843 - 5942	**0.020**
ICU stay	3549	0	806 - 6292	2934	0	1375 - 4493	0.687
Total readmission costs	1529	0	-994 - 4052	1129	0	333 - 1924	0.748
Total admission + readmission costs	13108	9217	8633 - 17583	13615	10260	10177 - 17053	0.855
Sensitivity analysis							
Postoperative admission costs*	8397	4943	4795 - 11999	9408	5493	6288 - 12527	0.67
Postoperative admission + readmission costs	9926	6136	5503 - 14350	10537	7413	7195 - 13878	0.823

All costs are presented in €. CI, confidence intervals. *excludes costs for primary operation and pathology

Table 4. Incremental costs, effects and ICERs of the outcomes of the study

	Incremental costs(€)	Incremental effects	ICER
Postoperative ileus	-507	0.21	-2414
Anastomotic Leakage	-507	0.06	-8450

ICER, incremental cost effectiveness ratio

Table 5. Sensitivity analysis of cost-effectiveness analysis

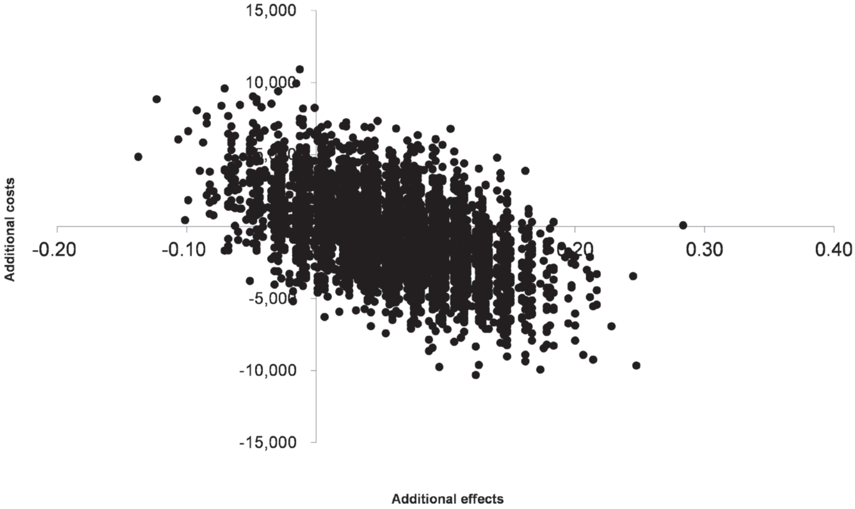
Outcome	Dominance	Inferiority
Postoperative admission costs		
Anastomotic leakage	65%	8%
Postoperative ileus	67%	1%
Postoperative admission + readmission costs		
Anastomotic leakage	57%	10%
Postoperative ileus	61%	1%

Probability of gum chewing being dominant or inferior compared to placebo when excluding costs for primary operation and pathology.

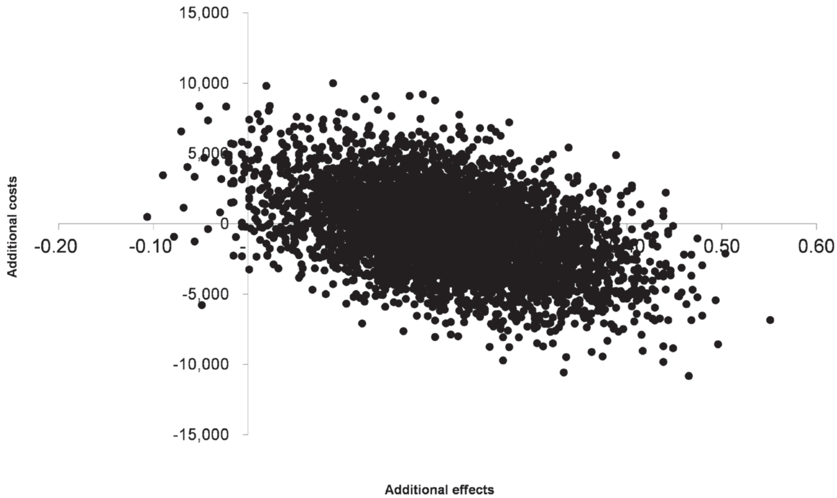
4.4.5. Cost-effectiveness analysis

Incremental costs, effects, and ICERs relating POI and AL were estimated using the total admission and readmission costs combined. The incremental mean costs divided by the incremental mean effects resulted in an ICER of -8,450 per AL and -2,414 per POI (Table 4). Both ICERs were negative, indicating that the gum chewing group dominated the control group due to lesser costs and positive effect (i.e. reduction in POI or AL).

The uncertainty analyses of the ICERs representing 5000 bootstrap replications are presented in the cost-effectiveness plane (Figure 1). For AL, 56% of the bootstrapped replications were located in the southeast quadrant, indicating the dominance of gum chewing (i.e positive effect at lesser costs), while 9% of the bootstrapped replications were located in the northwest quadrant, indicating inferiority (Figure 1a). For POI, the cost-effectiveness plane shows that 59% of the replications were located in the southeast quadrant, indicating dominance, while 1% of the replications were located in the northwest quadrant, indicating inferiority (Figure 1b).



(a)



(b)

Figure 1. (a) Cost-effectiveness of gum chewing versus placebo expressing costs per avoided incident of anastomotic leakage. (b) Cost-effectiveness plane of gum chewing versus placebo expressing costs per avoided incident of postoperative ileus

Figure 2 represents the CEAC for AL and POI. The probability of gum chewing being cost-effective in reducing POI and AL is >50% regardless of the applied threshold for willingness to pay. The sensitivity analyses for the cost-effectiveness analyses including only the postoperative costs are summarized in Table 5. Excluding costs for the primary operation and pathology analysis increased the probability of gum chewing being cost-effective for both POI and AL (Figure 3 and Figure 4).

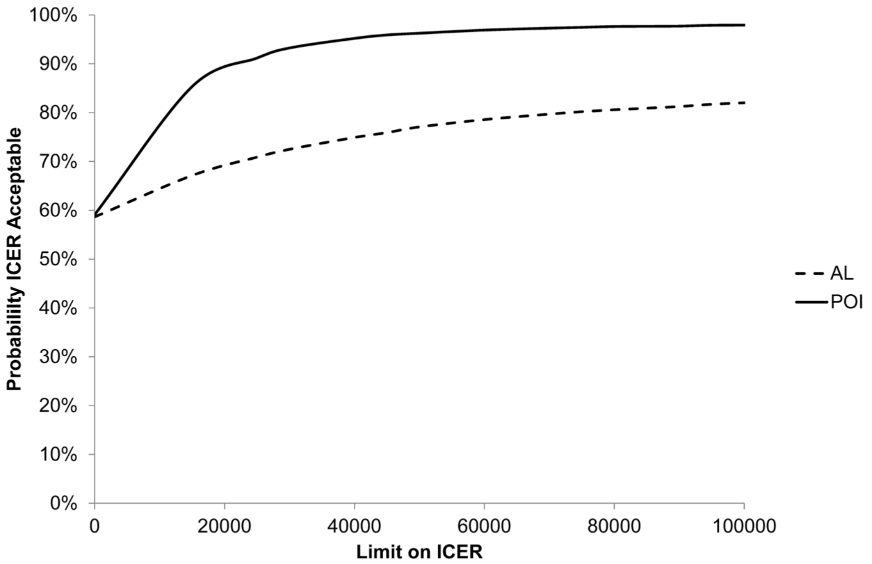


Figure 2. cost-effectiveness acceptability curves of postoperative ileus (POI) and anastomotic leakage (AL)

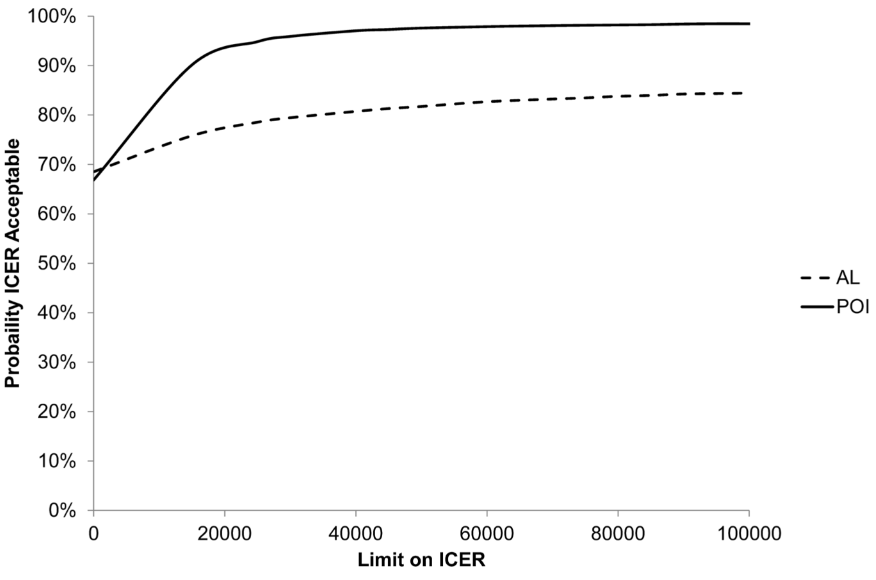


Figure 3. Sensitivity analysis of cost-effectiveness acceptability curves for postoperative admission costs (AL, anastomotic leakage; POI, postoperative ileus)

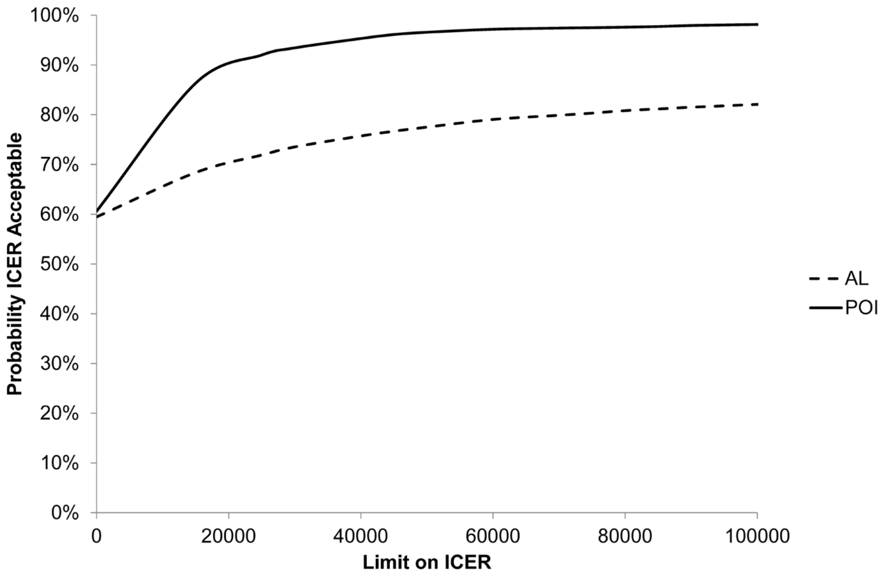


Figure 4. Sensitivity analysis of cost-effectiveness acceptability curves for postoperative admission + readmission costs (AL, anastomotic leakage; POI, postoperative ileus)

4.5. DISCUSSION

This study aimed to estimate the cost-effectiveness of perioperative gum chewing in colorectal cancer patients and to assess the effects on HRQoL, utilities, and in-hospital costs. Based on our data, gum chewing may be cost-effective in reducing POI, and to a lesser extent in reducing AL, while no clear benefit of gum chewing was observed on HRQoL, mapped utilities, and overall in-hospital costs. However, gum chewing was associated with a significant reduction in costs for ward stay.

The probability of gum chewing being dominant over the control was >50% for both POI and AL, regardless of the threshold value. In a recent randomized controlled trial comparing postoperative gum chewing (starting on day 1 after surgery) with standard care, Atkinson et al. found no differences in net monetary benefit between groups and concluded that gum chewing is unlikely to be cost-effective [19]. However, comparing the study by Atkinson and colleagues with our findings is inappropriate due to important differences between studies regarding (A) timing of gum chewing (postoperative [19] versus perioperative [4]), (B) clinical outcomes (no benefits of gum chewing [19] versus a reduction of POI and AL [4]), (C) cost perspective (societal [19] versus hospital [4]), and (D) measurement of effects in cost-effectiveness analysis (QALY [19] versus POI/AL [4]). Further studies are thus needed to compare the results of the current economic evaluation.

Perioperative gum chewing reduced costs for ward stay, but did not reduce overall costs. We hypothesize that the reduction in ward stay costs in the gum chewing group is directly linked to the reduction of POI and therefore shorter length of stay [4]. Both POI and AL are known to severely increase healthcare costs [5-7], as was visible in our data set when comparing total costs between patients with and without POI or AL (data not shown). As gum chewing conferred a reduction of both POI and AL [4], the lack of a significant difference between the groups in mean overall costs may be explained by the fact that the original study [4] was not powered to detect differences in costs. In addition, as opposed to cost-effectiveness analyses, the crude comparison between groups using p-values may not be the optimal method for detecting any cost-reducing effects of an intervention [18].

Surgery for colorectal cancer has been shown to improve quality of life 3 months after surgery [20]. Conversely, in our cohort, mean HRQoL scores and mapped utilities deteriorated in both groups after surgery. This may be explained by the fact that most patients completed the postoperative questionnaire within 10 days after surgery while still recovering from the surgical trauma regardless of complications. In general, QoL may not return to preoperative levels within the first 3 weeks after surgery even in the absence of complications [21], while postoperative complications can have both short- and long-term negative effects on QoL [9-12]. Reducing postoperative complications may limit the decrease in QoL shortly after surgery; however this could not be demonstrated in our data. Future studies with repeated QoL assessments using validated questionnaires at standardized time points are needed to provide more insight into the effects on postoperative QoL by interventions that reduce complications.

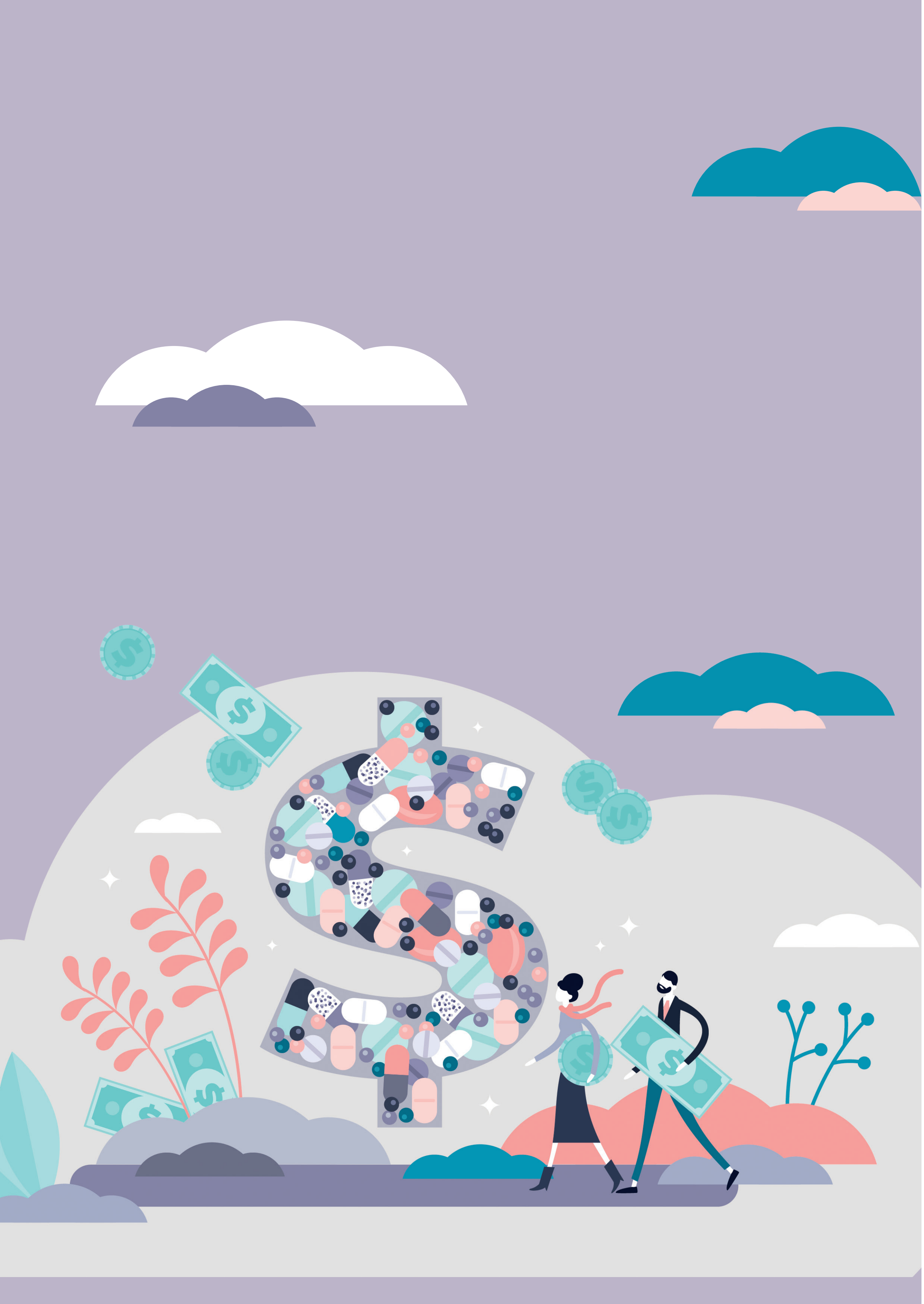
Several limitations are present in the current study. As noted, the original trial [4] was not powered to detect differences in in-hospital costs or quality of life, but rather on clinical outcomes. Moreover, there was a significant number of missing QLQ-C30 questionnaires and consequently the results were based on a limited sample size. The estimation of QALYs was inappropriate given the non-standardized time point for postoperative QoL assessment and the necessity of mapping the HRQoL scores to the required utility scores. A cost-utility analysis, as is recommended for current economic evaluation studies, could therefore not be performed. Furthermore, the obtained costs were from a hospital perspective only and productivity costs were not included. Lastly, this study was conducted as a trial-based economic evaluation, which may limit the generalizability of the results [22].

Overall, our data suggests that reducing POI and AL via perioperative gum chewing reduces costs for ward stay, but does not reduce overall in-hospital costs or confer a beneficial effect on HRQoL or mapped utilities. Although the CEAC curves suggest that gum chewing may be cost-effective for a wide range of threshold values, we cannot conclude with certainty that gum chewing is cost-effective in reducing POI or AL due to the limitations of our data. We recommend future studies with appropriate sample sizes to incorporate repeated assessments of QoL and utilities using validated questionnaires (e.g. EORTC QLQ C-30, EQ-5D-5L) at standardized time points. In addition, the use of a productivity cost questionnaire and medical cost questionnaire is recommended in order to include a societal perspective in cost-analyses.

REFERENCES*:*

1. Spanjersberg WR, Reurings J, Keus F, van Laarhoven CJ. Fast track surgery versus conventional recovery strategies for colorectal surgery. The Cochrane database of systematic reviews. 2011(2):CD007635.
2. Daams F, Luyer M, Lange JF. Colorectal anastomotic leakage: aspects of prevention, detection and treatment. World J Gastroenterol. 2013;19(15):2293-7.
3. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Br J Surg. 2015;102(5):462-79.
4. van den Heijkant TC, Costes LM, van der Lee DG, Aerts B, Osinga-de Jong M, Rutten HR, et al. Randomized clinical trial of the effect of gum chewing on postoperative ileus and inflammation in colorectal surgery. Br J Surg. 2015;102(3):202-11.
5. Ashraf SQ, Burns EM, Jani A, Altman S, Young JD, Cunningham C, et al. The economic impact of anastomotic leakage after anterior resections in English NHS hospitals: are we adequately remunerating them? Colorectal Dis. 2013;15(4):e190-8.
6. Iyer S, Saunders WB, Stemkowski S. Economic burden of postoperative ileus associated with colectomy in the United States. Journal of managed care pharmacy : JMCP. 2009;15(6):485-94.
7. Govaert JA, Fiocco M, van Dijk WA, Scheffer AC, de Graaf EJ, Tollenaar RA, et al. Costs of complications after colorectal cancer surgery in the Netherlands: Building the business case for hospitals. Eur J Surg Oncol. 2015;41(8):1059-67.
8. Barletta JF, Senagore AJ. Reducing the burden of postoperative ileus: evaluating and implementing an evidence-based strategy. World J Surg. 2014;38(8):1966-77.
9. Brown SR, Mathew R, Keding A, Marshall HC, Brown JM, Jayne DG. The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. Annals of surgery. 2014;259(5):916-23.
10. Bloemen JG, Visschers RG, Truin W, Beets GL, Konsten JL. Long-term quality of life in patients with rectal cancer: association with severe postoperative complications and presence of a stoma. Dis Colon Rectum. 2009;52(7):1251-8.
11. Bosma E, Pullens MJ, de Vries J, Roukema JA. The impact of complications on quality of life following colorectal surgery: a prospective cohort study to evaluate the Clavien-Dindo classification system. Colorectal Dis. 2016;18(6):594-602.
12. Marinatou A, Theodoropoulos GE, Karanika S, Karantanos T, Siakavellas S, Spyropoulos BG, et al. Do anastomotic leaks impair postoperative health-related quality of life after rectal cancer surgery? A case-matched study. Dis Colon Rectum. 2014;57(2):158-66.
13. Gold MR. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996. xxiii, 425 p. p.
14. Vather R, Trivedi S, Bissett I. Defining postoperative ileus: results of a systematic review and global survey. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2013;17(5):962-72.
15. Fayers PM AN, Bjordal K, Groenvold M, Curran D, Bottomley A, on, Group. botEQoL. The EORTC QLQ-C30 Scoring Manual (3rd Edition). European Organisation for Research and Treatment of Cancer,Brussels. 2001.

16. Versteegh MM, Leunis A, Luime JJ, Boggild M, Uyl-de Groot CA, Stolk EA. Mapping QLQ-C30, HAQ, and MSIS-29 on EQ-5D. Medical decision making : an international journal of the Society for Medical Decision Making. 2012;32(4):554-68.
17. Bleichrodt H, Quiggin J. Life-cycle preferences over consumption and health: when is cost-effectiveness analysis equivalent to cost-benefit analysis? Journal of health economics. 1999;18(6):681-708.
18. Mani K, Lundkvist J, Holmberg L, Wanhainen A. Challenges in analysis and interpretation of cost data in vascular surgery. Journal of vascular surgery. 2010;51(1):148-54.
19. Atkinson C, Penfold CM, Ness AR, Longman RJ, Thomas SJ, Hollingworth W, et al. Randomized clinical trial of postoperative chewing gum versus standard care after colorectal resection. Br J Surg. 2016;103(8):962-70.
20. Ronning B, Wyller TB, Nesbakken A, Skovlund E, Jordhoy MS, Bakka A, et al. Quality of life in older and frail patients after surgery for colorectal cancer-A follow-up study. J Geriatr Oncol. 2016;7(3):195-200.
21. Dowson HM, Ballard K, Gage H, Jackson D, Williams P, Rockall TA. Quality of life in the first 6 weeks following laparoscopic and open colorectal surgery. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2013;16(2):367-72.
22. Drummond M, Manca A, Sculpher M. Increasing the generalizability of economic evaluations: recommendations for the design, analysis, and reporting of studies. International journal of technology assessment in health care. 2005;21(2):165-71.



CHAPTER 5

An economic evaluation of perioperative enteral nutrition in patients undergoing colorectal surgery (SANICS II study)

Published as:
Pattamatta M, Evers SMAA, Smeets BJJ, Peters EG, Luyer MDP, Hiligsmann M. An economic evaluation of perioperative enteral nutrition in patients undergoing colorectal surgery (SANICS II study). Journal of Medical Economics. 2019 Mar;22(3):238-244. doi: 10.1080/13696998.2018.1557200.

ABSTRACT

Aims: The objective of this (trial-based) economic evaluation was to assess, from a societal perspective, the cost- effectiveness of perioperative enteral nutrition compared with standard care in patients undergoing colorectal surgery.

Methods: Alongside the SANICS II randomized controlled trial, global quality of life, utilities (measured by EQ-5D-5L), healthcare costs, production losses and patient and family costs were assessed at baseline, 3 months and 6 months. Incremental cost-effectiveness ratios (ICERs) (i.e. cost per increased global quality of life score or quality-adjusted life year (QALY) gained) and cost-effectiveness acceptability curves were visualized.

Results: In total, 265 patients were included in the original trial (n=132 in the perioperative enteral nutrition group and n=133 in the standard care group). At 6 months, global quality of life (83 versus 83, $p=0.357$) did not differ significantly between the groups. The mean total societal costs for the intervention and standard care groups were €14,673 and €11,974 respectively but did not reach the statistical significance (p=0.109). The intervention resulted in an ICER of -€6276 per point increase in the global quality of life score. The gain in QALY was marginal (0.003) with an additional cost of €2,941 and the ICUR (Incremental cost utility ratio) was estimated at €980,333.

Limitations: The cost elements for all the participating centers reflect the reference prices from the Netherlands. Patient-reported questionnaires may have resulted in recall bias. Sample size was limited by exclusion of patients who did not complete questionnaires at least at two time points. A power analysis based on costs and health-related quality of life (HRQoL) was not performed. The economic impact could not be analyzed at 1 month postoperatively where the effects could potentially be higher.

Conclusions: This study suggests that perioperative nutrition is not beneficial for the patients in terms of quality of life and is not cost effective.

5.1. INTRODUCTION

Postoperative outcomes following colorectal surgery have tremendously improved as a result of the implementation of fast-track protocols.[1] Despite these beneficial results, anastomotic leakage (AL) and postoperative ileus (POI) are still important determinants of postoperative morbidity (1- 19% and 27-48% respectively).[1-4] Postoperative complications strongly increase healthcare costs and can negatively impact both short- and long-term quality of life (QoL).[5-10]

In previous clinical studies, POI was reduced (from 35% to 16%) when enteral nutrition was started very early after rectal surgery.[11] A recent randomized controlled trial (SANICS II trial) was conducted to assess the clinical and economic effects of perioperative lipid-enriched enteral nutrition versus standard care following colorectal surgery. [12] This trial demonstrated that perioperative enteral nutrition (PEN) did not significantly reduce postoperative complications.[12] Although there is no demonstrated advantage of PEN in terms of postoperative complications, it is important to study the impact of the intervention on societal costs and health-related quality of life which (HRQoL) could potentially be different. Furthermore, it is important to investigate the (societal) costs of such an intervention, that in some specific surgical patients with higher inflammatory response, could be more beneficial. Economic considerations are nowadays increasingly important in our healthcare system to help decision makers to efficiently allocate resources. This study is therefore a report on the total societal costs, quality of life and on the cost-effectiveness of the intervention perioperative lipid-enriched enteral nutrition versus standard care following colorectal surgery.

The aim of this study was thus to compare, from a societal perspective, the cost-effectiveness (i.e. cost per point increase in global quality of life score, measured using EORTC QLQ-C30 questionnaires) and cost-utility (i.e. cost per quality-adjusted life years [QALY] gained) of the PEN with standard care (control) in patients undergoing colorectal surgery over a period of 6 months.

5.2. METHODS

5.2.1. Design

This trial-based economic evaluation is embedded in a randomized controlled trial in which the clinical effectiveness of PEN was previously assessed. [12] The original study was a multicentre double-blind, randomized controlled trial that was conducted in three large Dutch hospitals and two Danish hospitals. The trial was designed to compare lipid-rich nutrition administrated just before, during and after colorectal resection to standard care (no nutrition). The original study was approved by the Medical Ethics Committee of the Catharina Hospital (Eindhoven, The Netherlands). The principles of Good Clinical Practice and the Declaration of Helsinki were followed. The trial was registered with ClinicalTrials.gov (number NCT02175979) and trialregister.nl (number NTR4670). All patients provided written informed consent. Further details regarding the trial and the clinical results can be found elsewhere. [12]

The economic evaluation was performed according the Dutch guideline for economic evaluation[13] and the Consolidated Health Economic Evaluation Reporting Standards.[14]

5.2.2. Participants and setting

All patients recruited to the SANICS II trial described earlier were considered for inclusion in the current study. Briefly, patients were eligible for inclusion if aged 18 or older and undergoing elective segmental colorectal resection with primary anastomosis. The exclusion criteria were previous gastric or oesophageal resection, peritoneal metastases, an ileostomy, and the use of glucocorticosteroids or medication that disrupted acetylcholine metabolism (e.g., selective serotonin reuptake inhibitors or anticonvulsants). The patients were not identified to be malnourished and were randomly assigned to the intervention or standard care group and stratification was applied to ensure an equal distribution between colonic and rectal surgery and between laparoscopic and open procedures.

5.2.3. Interventions

Detailed information on the intervention and its composition is found in the original article.[12] All the patients received a self-migrating naso-jejunal tube and were connected to a tubing system. The tubing system was opaque and bifurcated into two branches. One branch was connected to the tube in the patient and the other branch was occluded at the bifurcation by the manufacturer. For patients in the intervention group, the tubing system was open towards the patient and closed towards the blinded container.

Conversely, for patients allocated to the standard care group, the tubing system was closed towards the patient and open towards the blinded container. Consequently, only patients in the intervention group received the lipid enriched nutrition. Patients received continuous lipid enriched enteral tube feeding from 3 hours before until 6 hours after surgery. This special nutrition (Nutricia Research, Utrecht, Netherlands) was composed of chemicals, minerals and vitamins. Patients allotted to the standard care group did not receive PEN and were treated to ERAS (Enhanced Recovery After Surgery) guidelines.

5.2.4. Economic evaluation

A cost-effectiveness analysis and cost utility analysis were performed in this study. Self-reported questionnaires were administrated to all patients at baseline, 3 months and 6 months.

The outcome of the cost-effectiveness analysis (CEA) was global quality of life retrieved from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) questionnaires. Six-month mean values were calculated using T0, T1 and T2 scores. The EORTC QLQ-C30 is a cancer specific questionnaire that includes the function domains (physical, emotional, social, role and cognitive), eight symptoms (fatigue, pain, nausea/vomiting, constipation, diarrhea, insomnia, dyspnea and appetite loss) as well as global health/quality of life and financial impact. Each dimension was scored on a four point scale from “not at all” to “very much” for most items. Raw scores are converted to a 0-100 scales with higher scores reflecting higher levels of function and higher level of symptom burden. Patients with non-malignant nature of the disease were excluded from this cost-effectiveness analysis.

The outcome of the cost-utility analysis (CUA) was QALY as it is the preferred and the most common outcome in economic evaluation. QALYs were calculated by means of the “area under the curve” method, in which the time in a certain health state was multiplied by the utility of this health state.[15] It was measured with EQ-5D-5L questionnaire which is the international standard for utility measurement[16] and consists of five dimensional Euroqol (EQ-5D-5L) comprising of mobility, selfcare, usual activities, pain/discomfort and anxiety/depression. Each dimension was scored on five-point scale which represented ‘no problems’, ‘slight problems’, ‘moderate problems’, ‘severe problems’, and ‘extreme problems’. Utilities were derived from EQ-5D-5L using Dutch tariffs.[16] The five dimensions can be summed into a health state. Utility values were calculated for these health states, using preferences elicited from a general population, the so called Dutch algorithm.[16]

5.2.5. Costs

Cost data were collected at 3 months and 6 months. Costs were calculated from a societal perspective meaning that all costs and (monetary) benefits were included regardless of who pays the costs or who gain the benefits. The iMTA Medical consumption questionnaire (iMCQ) was used to measure the healthcare utilization and the iMTA productivity cost questionnaire (iPCQ)[17] was used to measure the costs due to productivity losses in two domains related to 1) paid work due to absenteeism and presenteeism, and 2) unpaid work.[17] The recall period for the iMCQ is 3 months and for the iPCQ is 4 weeks.

Costs were divided into three categories: healthcare sector costs, costs for patient and family and productivity costs. Healthcare costs consisted of medication costs, consultations with healthcare professionals, use of diagnostic methods, frequency of inpatient stay and outpatient treatment. The calculation of healthcare costs was based on identified health services consumed by the patient and was multiplied with their corresponding unit prices. Total costs were estimated by summing individual services. The updated Dutch manual for Costing Analysis in Healthcare Research was used for the valuation of the healthcare costs.[13] All medication costs were derived from the website with official listing of drugs with prices: www.medicijnkosten.nl. Medication costs were based on the price per dosage of the drug in the Netherlands. In case of uncertainty, a lowest cost price was used. Medications without a specific name were omitted (for example, when patient mentions antibiotics or “medicine for stomach protection”). Patient and family costs included the use of formal (paid care) and informal care. The costs for unpaid care were valued using the proxy good method, which values the time spent on informal care at the labor market price of a close market substitute. Productivity costs included productivity losses due to absence from work and were valued using friction cost method as recommended by Dutch guidelines.[13] The friction cost method takes into account production losses confined to the period needed to replace the sick employee (85 days).[18]. All costs were indexed for the year 2017. The study follow-up was 6 months and therefore no discounting was performed (for either costs or effects).

5.3. ANALYSES

Analyses were conducted using IBM SPSS Statistics version 24.0 for Windows(IBM corp., Armonk, NY, USA). Normally distributed data are presented as means (standard deviation) and were tested using the unpaired t-test, while non-parametric data are presented as median [range] and were tested using the Mann-Whitney U test. Baseline differences in costs were checked with nonparametric bootstrapping, based on 1000 replications.

Patients were excluded from the analysis when two or more questionnaires (cost and quality of life questionnaires) were missing at more than one time point. Missing values (i.e., EQ-5D-5L, EORTC QLQ C-30 and costs) were managed using mean imputations.

Incremental cost-effectiveness ratios (ICERs) and incremental cost utility ratios (ICURs) were estimated as the difference in costs between PEN and standard care divided by their differences in their effects or QALYs resulting in the costs per improved quality of life or costs per QALY. To quantify the uncertainty around the ICER, non-parametric bootstrapping was conducted in Microsoft Excel (5000 simulations).

Cost-effectiveness acceptability curves (CEAC) were used to present the results of the bootstrapping. A CEAC is a graphic representation of the uncertainty in differences in costs and effects between the two groups, showing the probability of an intervention being cost-effective for a wide range of threshold values. In the Netherlands, the council for Public Health and Healthcare proposed an informal ceiling ratio for the QALYs between €20,000 and €80,000 per QALY, depending on the burden of the disease.[19]

Two one-way sensitivity analyses were performed to test the robustness of the results. The first analysis assessed the impact of imputation, thus included complete case only. Patients with missing variables were dropped from the analysis leaving only complete cases. A total of 183 patients (94 patients in the PEN group and 89 patients in the standard care) were included for both complete case cost-effectiveness analysis and cost utility analysis

The second analysis assessed the effects of including the excluded patients in the cost-effectiveness analysis due to non-malignant nature of their disease (n=15). Fifteen patients were excluded in the base case cost-effectiveness analysis due their non-malignant tumor. A second sensitivity analysis was performed including these cases (n=233).

5.4. RESULTS

5.4.1. Baseline characteristics

Between August 2014 and August 2017, 265 patients were included in the original trial (n= 132 in the PEN group and n=133 in the standard care group). Of this, 259 patients (97.7%) completed the questionnaires at baseline, 224 (84.5%) patients completed postoperatively at 3 months and 216 (81.5%) patients completed at 6 months. Thirty-two patients with missing questionnaires at least at two time points were excluded from the analysis. Furthermore, 15 patients with a non-malignant disease were excluded from the EORTC analysis. Ultimately, 233 patients were included in cost-utility analysis (120 patients in PEN group and 113 patients in standard care group) and 218 patients in the EORTC base case analysis and cost-effectiveness analysis (116 patients in the PEN group and 102 patients in the standard care group).

5.4.2. EORTC QLQ-C30 scores and utilities

There were no significant differences between the groups in any functioning, symptom or quality of life scales. Most scores (except the emotional functioning score) and utilities at 3 and 6 months deteriorated in both the groups in comparison with scores at baseline. Pre- and postoperative scores and utilities are summarized in Table 1.

Table 1. Health-related quality of life (EORTC QLQ-C30) and utility scores in perioperative enteral nutrition versus control

	Preoperative (N = 218)			**Postoperative 3 months(N = 218)**			**Postoperative 6 months (N = 218)**		
Dimension	Intervention(116)	Control(102)	P-value	Intervention(116)	Control(102)	P-value	Intervention(116)	Control(102)	P-value
Global quality of life	83 [16 - 100]	83 [16 - 100]	0.649	77 ± 16	77 ± 17	0.843	83[16 - 100]	83 [0 - 100]	0.357
Physical functioning	93 [0 - 100]	93 [6 - 100]	0.941	86 [33 - 100]	86 [6 - 100]	0.85	86 [26 - 100]	86 [6 - 100]	0.605
Role functioning	100 [0 - 100]	100 [0 - 100]	0.242	83 [0 - 100]	83 [0 - 100]	0.856	83 [0 - 100]	83 [0 - 100]	0.835
Emotional functioning	83 [16 - 100]	83 [8 - 100]	0.571	100 [25-100]	100 [66 - 100]	0.755	91[41 -1006]	100 [25 - 100]	0.511
Cognitive functioning	100 [33 - 100]	100 [0 - 100]	0.063	100 [16 - 100]	100 [33 - 100]	0.179	100 [16 - 100]	100 [16 - 100]	0.816
Social functioning	100 [0 - 100]	100 [33 - 100]	0.244	100 [0 - 100]	100 [0 - 100]	0.490	100 [33 - 100]	100 [0 - 100]	0.965
Fatigue	88 [22 - 100]	88 [0 - 100]	0.592	77 [0 - 100]	77 [0 - 100]	0.223	77 [0 - 100]	77 [0 - 100]	0.977
Nausea/vomiting	0 [0 - 66]	0 [0 - 66]	0.085	0 [0 - 50]	0 [0 66]	0.820	0 [0 - 83]	0 [0 - 100]	0.869
Pain	0 [0 -100]	0 [0-100]	0.787	0 [0 - 83]	33 [0 - 83]	0.866	0 [0 - 100]	0 [0 - 100]	0.613
Dyspnea	0 [0 - 100]	0 [0 - 66]	0.689	0 [0 - 100]	0 [0 - 100]	0.704	0 [0 - 66]	0 [0 - 66]	0.613
Insomnia	0 [0 - 100]	0 [0 - 100]	0.473	0 [0 - 100]	0 [0 - 100]	0.196	0 [0 - 100]	0 [0 - 100]	0.543
Appetite loss	0 [0 -100]	0 [0 - 100]	0.723	0 [0 - 100]	0 [0 - 66]	0.383	0 [0 - 100]	0 [0 - 100]	0.524
Constipation	0 [0 - 100]	0 [0 - 100]	0.41	0 [0 - 66]	0 [0 - 100]	0.685	0 [0 - 66]	0 [0 - 100]	0.393
Diarrhea	0 [0 - 66]	0 [0 - 100]	0.263	0 [0 - 100]	0 [0 - 100]	0.507	0 [0 - 100]	0 [0 - 100]	0.850
Financial problems	0 [0 - 66]	0 [0 - 66]	0.397	0 [0 - 66]	0 [0 - 66]	0.367	0 [0 - 66]	0 [0 - 66]	0.914
Utilities	0.91 [0.03 - 1]	0.89 [0.23 - 1]	0.400	0.85[0.24 - 1]	0.89 [0.23 - 1]	0.310	0.89 [0.07 - 1]	0.85 [-0.29 - 1]	0.470

Values are mean ± standard deviation or median [range]

5.4.3. Costs

The total societal costs in the 6 months following the surgery were €14,673 and €11,974 for the PEN and standard care group respectively, although non-significance was observed (p=0.109). Hospital stay costs and costs due to productivity losses were €2,853 versus €2,089 at p=0.194 and €3,205 versus €1,897 at p=0.130 for the PEN and standard care group respectively. The cost distribution of the two groups is shown in Table 2.

Table 2. Resources used and mean costs with bootstrapped 95% confidence intervals during the 6-month period

Resources	Perioperative nutrition (n=120)	Control (n=113)	P-value
Intervention costs	272	0	
Healthcare costs			
General practitioner	72	92	0.212
Medications	465	517	0.781
Outpatient clinic	455	498	0.506
Allied health professionals	200	204	0.925
Home care	659	625	0.892
Hospital stay	2,853	2,089	0.194
Emergency room visits	53	93	0.073
Ambulance	38	51	0.628
Diagnostics	60	66	0.833
Treatment	139	209	0.522
Revalidation therapy	59	91	0.572
Total healthcare costs	5,055 [4,073 - 6,105]	4,542 [3,604 - 5,461]	0.509
Productivity costs			
Paid home care	2,985	1,682	0.129
Inability to do unpaid labour	219	215	0.950
Total productivity losses	3,205 [2,030 - 4,492]	1,897 [1,061 - 2,933]	0.130
Total costs	14,673 [12,492 - 16806]	11,974 [9,533 - 13,988]	0.109

*Mean[confidence interval: 2.5th percentile and 7.5th percentile]; All costs are presented in €

5.4.4. Cost-effectiveness and cost utility analysis

Concerning the global quality of life, the intervention resulted in an additional cost of 2,699 and a lower global quality of life. The ICER was estimated inferior at -€6,276 (11,974-14,673/77.52-77.09) per point increase of global quality of life. With respect to the QALY, the intervention resulted in an additional cost of €2,941 and a marginal increase in QALY (0.003). The ICUR was estimated at €980,333 (14,633-11,692/0.432-0.429) showing that the intervention is not a cost- effective treatment compared with the standard care. The marginal additional benefit on QALY produced by the intervention comes at an high additional cost of €2941. Results of bootstrap replications of ICERs/ICURs are presented in Figure 1 and Figure 2 which presents the difference in costs and effects between the PEN and standard care for each bootstrap replication.

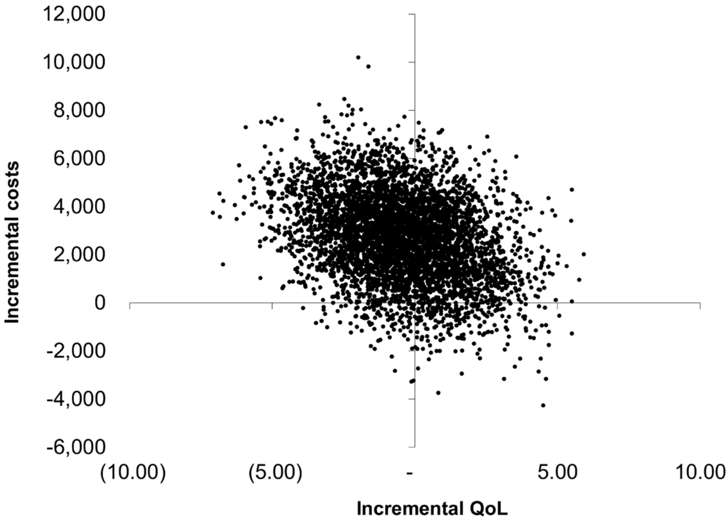


Figure 1. Cost-effectiveness of perioperative enteral nutrition versus standard care per point increase in global quality of life. QoL, quality of life.

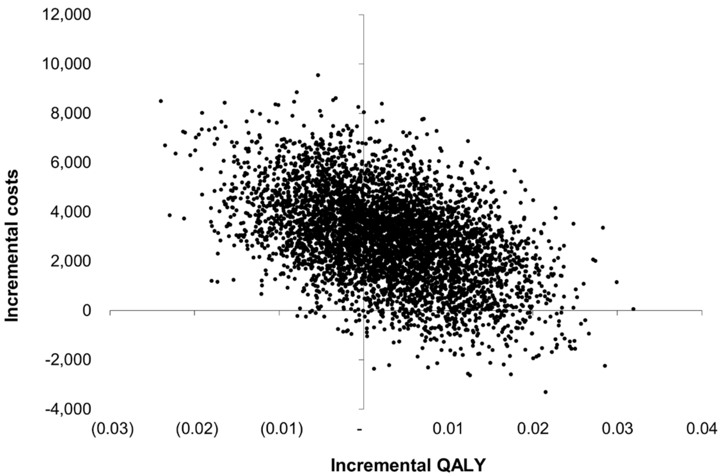


Figure 2. Cost-effectiveness plane of perioperative enteral nutrition versus standard care per point increase in QALY gained. QALY, quality-adjusted life years.

The probability that the PEN is cost effective given different ceiling ratios, as presented in CEACs is shown in Figure 3. In terms of QALYs, if the willingness to pay is €50,000 per QALY gained, the probability that PEN would be cost effective is 9% (Figure.4).

The results of sensitivity analysis were similar to the base case analysis. Excluding the imputed cases or including the non-malignant cases (with respect to global quality of life) did not increase the probability of PEN being cost effective. The results of the sensitivity analysis for cost-effectiveness and cost utility analysis are summarised in Table 3.

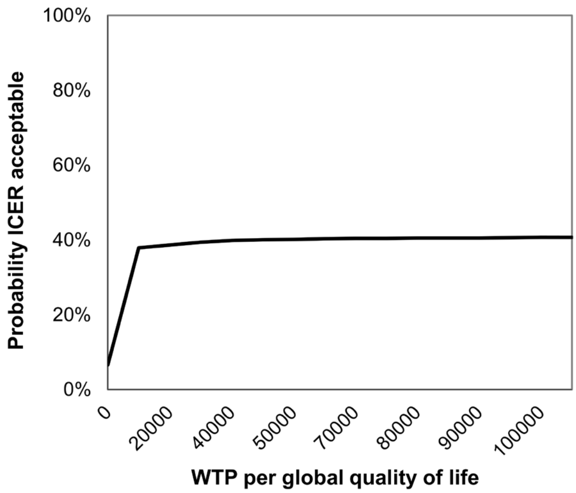


Figure 3. Cost-effectiveness acceptability curve of costs per point increase in global quality of life. WTP, willingness to pay; ICER, incremental cost-effectiveness ratio.

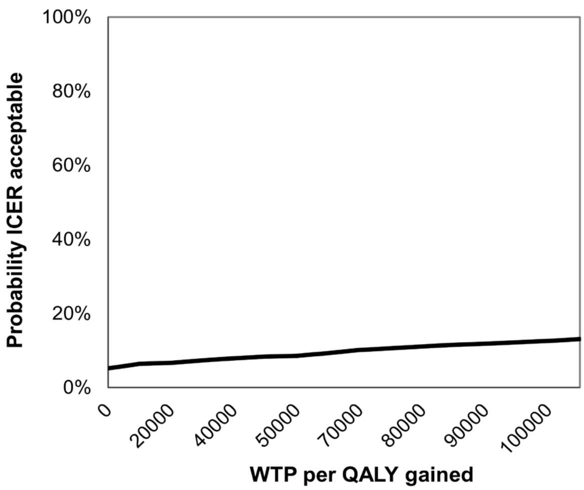


Figure 4. Cost-effectiveness acceptability curve of costs per QALY gained. WTP, willingness to pay; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

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Table 3. Sensitivity analysis of cost-effectiveness (complete case global quality of life and global quality of life including non-cancer cases) and cost utility analysis (complete case QALY)

	Perioperative enteral nutrition		**Control**		**Incremental costs(€)**	**Incremental Effects**	**ICER**
	Cost(€)	Effect	Cost(€)	Effect			
Complete case Global quality of life	14,652	77.480	11,726	78.600	2,925	-1.110	-2,635
Complete case QALY	14,652	0.436	11,726	0.433	2,925	0.003	975,000
Global quality of life including non cancer cases	14,361	77.380	11,692	77.890	2,668	-0.510	-5,238

QALY, quality adjusted life years; ICER, incremental cost effectiveness ratio

5.5. DISCUSSION

The study aimed to estimate the cost-effectiveness of PEN in patients undergoing colorectal surgery. Based on this trial data, PEN is not cost effective compared to usual care. It even increases the societal costs while not contributing in improving the quality of life in patients after colorectal surgery.

Although, there is no definite willingness to pay threshold known for improvement on the global quality of life scores, the estimates show that intervention was <41% at various threshold values and hence the probability of intervention being cost effective is low. Regarding QALYs, the probability that PEN being cost effective at a threshold of 50,000 was only 9% which is not a promising estimate.

There was a substantial increase in the paid home care costs in the intervention group. PEN also resulted in higher societal costs. This may be due to increased hospital stay costs and productivity costs. We hypothesize that this finding may be linked to the (unexpected) increased rate in complications (such as pneumonia). This finding was not in line with a recent study by Rinninella et al [20].

In a retrospective analysis of patients consequently enrolled in an intervention group [ERAS (Enhanced Recovery After Surgery)+Nutricatt protocol] were comparing with patients treated according to standard ERAS protocol. The Nutricatt protocol consisted of nutritional prehabilitation before surgery and in the perioperative period. Here, a significant decrease in the hospital costs, complication associated costs and length of stay in the intervention group was found [20].

However, comparing the study by Rinninella with our study may not be completely appropriate due to important differences between the studies regarding (A) Comparison with the control group (retrospective cohort versus randomization), (B) Nutritional support (starting from 3 weeks before admission, pre- and postoperative and one month outpatient visit versus perioperative nutritional supplement), (C) composition of the nutritional supplements (oral diet versus lipid enriched nutrition in the perioperative period).[20]

In the current study, there was no improvement in the HRQoL scores. This may again be explained by the fact that the postoperative complications did not improve after the surgery and reducing the complications may limit the decrease in QoL after surgery; however this could not be demonstrated in our data.

The primary strength of this analysis is that patient level data from a randomized controlled trial was used. In addition, the economic evaluation was performed from the preferred (societal) perspective.

There are however some limitations in the study. 1. The cost elements for all the participating centers reflect the reference prices from the Netherlands . 2. The use of patient reported questionnaires may have resulted in recall bias. 3. The study was conducted as a trial-based economic evaluation which may limit the generalizability of the results.[21] 4. Sample size was limited by exclusion of patients in the initial group who did not complete questionnaires at least at two time points. Additionally, a power analysis based on costs and HRQoL was not performed and this could potentially explain the non-significance of some results. 5. Since the patients were administered with questionnaires at baseline, 3 months and 6 months, it was impossible to do an analysis and check the economic impact at 1 month postoperatively where the effects could potentially be higher.

In conclusion, this trial-based economic evaluation suggests that PEN is not cost effective compared to usual care and does not confer a beneficial effect in HRQoL or utilities. Further studies are needed to confirm this finding and also to elucidate whether subgroups may benefit from this intervention.

REFERENCES:

1. Spanjersberg WR, Reurings J, Keus F, van Laarhoven CJ. Fast track surgery versus conventional recovery strategies for colorectal surgery. The Cochrane database of systematic reviews. 2011(2):Cd007635.
2. Daams F, Luyer M, Lange JF. Colorectal anastomotic leakage: aspects of prevention, detection and treatment. World J Gastroenterol. 2013;19(15):2293-7.
3. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Br J Surg. 2015;102(5):462-79.
4. van den Heijkant TC, Costes LM, van der Lee DG, Aerts B, Osinga-de Jong M, Rutten HR, et al. Randomized clinical trial of the effect of gum chewing on postoperative ileus and inflammation in colorectal surgery. Br J Surg. 2015;102(3):202-11.
5. Ashraf SQ, Burns EM, Jani A, Altman S, Young JD, Cunningham C, et al. The economic impact of anastomotic leakage after anterior resections in English NHS hospitals: are we adequately remunerating them? Colorectal Dis. 2013;15(4):e190-8.
6. Iyer S, Saunders WB, Stemkowski S. Economic burden of postoperative ileus associated with colectomy in the United States. J Manag Care Pharm. 2009;15(6):485-94.
7. Govaert JA, Fiocco M, van Dijk WA, Scheffer AC, de Graaf EJ, Tollenaar RA, et al. Costs of complications after colorectal cancer surgery in the Netherlands: Building the business case for hospitals. Eur J Surg Oncol. 2015;41(8):1059-67.
8. Barletta JF, Senagore AJ. Reducing the burden of postoperative ileus: evaluating and implementing an evidence-based strategy. World J Surg. 2014;38(8):1966-77.
9. Brown SR, Mathew R, Keding A, Marshall HC, Brown JM, Jayne DG. The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. Annals of surgery. 2014;259(5):916-23.
10. Bloemen JG, Visschers RG, Truin W, Beets GL, Konsten JL. Long-term quality of life in patients with rectal cancer: association with severe postoperative complications and presence of a stoma. Dis Colon Rectum. 2009;52(7):1251-8.
11. Boelens PG, Heesakkers FF, Luyer MD, van Barneveld KW, de Hingh IH, Nieuwenhuijzen GA, et al. Reduction of postoperative ileus by early enteral nutrition in patients undergoing major rectal surgery: prospective, randomized, controlled trial. Annals of surgery. 2014;259(4):649-55.
12. Peters EG, Smeets BJJ, Nors J, Back CM, Funder JA, Sommer T, et al. Perioperative lipid-enriched enteral nutrition versus standard care in patients undergoing elective colorectal surgery (SANICS II): a multicentre, double-blind, randomised controlled trial. The lancet Gastroenterology & hepatology. 2018;3(4):242-51.
13. Kanters TA, Bouwmans CA, van der Linden N, Tan SS, Hakkaart-van Roijen L. Update of the Dutch manual for costing studies in health care. PloS one. 2017;12(11):e0187477.
14. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. International journal of technology assessment in health care. 2013;29(2):117-22.
15. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes: Oxford university press; 2015.

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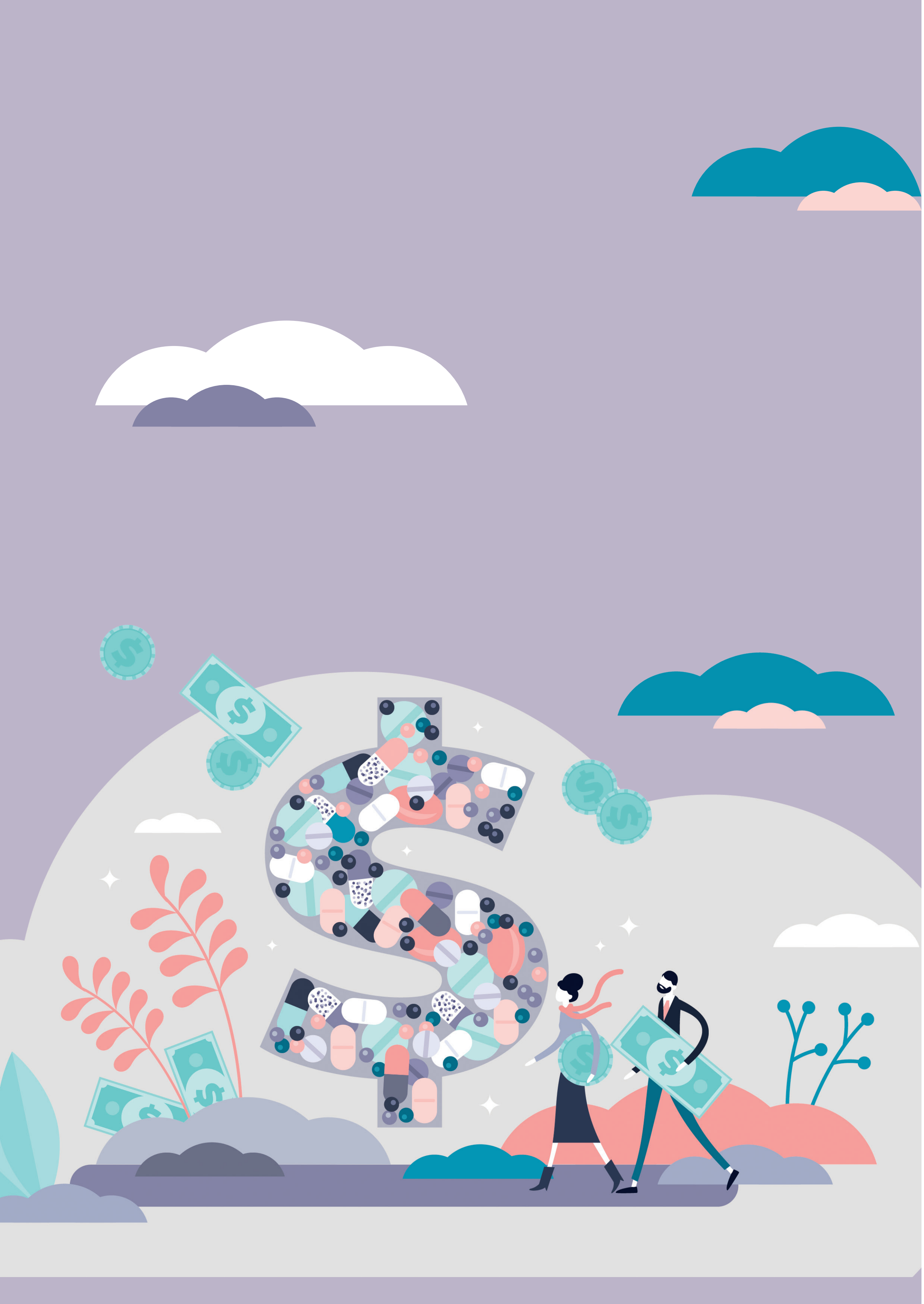
16. Versteegh MM, Vermeulen KM, Evers SM, de Wit GA, Prenger R, Stolk EA. Dutch tariff for the five-level version of EQ-5D. Value in health. 2016;19(4):343-52.
17. Bouwmans C, Krol M, Brouwer W, Severens JL, Koopmanschap MA, Hakkaart L. IMTA Productivity Cost Questionnaire (IPCQ). Value Health. 2014;17(7):A550.
18. Hakkaart-van Roijen L, Van der Linden N, Bouwmans C, Kanters T, Tan SS. Kostenhandleiding. Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg In opdracht van Zorginstituut Nederland Geactualiseerde versie. 2015.
19. *Sensible and sustainable care*. Council for Public Health and Health Care. 2006.
20. Rinninella E, Persiani R, D'Ugo D, Pennestri F, Cicchetti A, Di Brino E, et al. NutriCatt protocol in the Enhanced Recovery After Surgery (ERAS) program for colorectal surgery: The nutritional support improves clinical and cost-effectiveness outcomes. Nutrition. 2018;50:74-81.
21. Drummond M, Manca A, Sculpher M. Increasing the generalizability of economic evaluations: recommendations for the design, analysis, and reporting of studies. International journal of technology assessment in health care. 2005;21(2):165-71.



CHAPTER 6

Effect of direct oral feeding following minimally invasive esophagectomy on costs and quality of life

Published as:
Pattamatta M, Fransen LFC, Dolmans-Zwartjes ACP, Nieuwenhuizen GAP, Evers SMAA, Kouwenhoven EA, Det MJ van, Hiligsmann M, Luyer MDP. Effect of direct oral feeding following minimally invasive esophagectomy on costs and quality of life. Journal of Medical Economics. 2020 Dec;(in press). doi: 10.1080/13696998.2020.1859843.

ABSTRACT

Aims: Following (minimally invasive) esophagectomy, patients often rely on tube feeding, since oral intake is often delayed. Consequently, additional support by a dietician and home care is needed until oral intake is commenced. In this study, the effects of direct start of oral feeding compared with tube feeding following an esophagectomy was evaluated on treatment costs and health-related quality of life (QoL).

Methods: Patients undergoing a minimally invasive esophagectomy were randomized in the NUTRIENT II study between controls (nil-per-mouth during 5 days and subsequent tube feeding) and a group in whom oral feeding was started directly postoperatively. Total hospital costs (including readmission and outpatient costs) and home care data for a period of 6 months after surgery were analyzed. QoL (measured using EORTC-QLQ-C30 and EORTC OG-25) was assessed preoperatively and 6 weeks, 12 weeks, and 6 months postoperatively.

Results: A total 132 patients were included (n=65 direct oral feeding group and n=67 control group). Mean patient hospital costs were €26,014 in the intervention group over a 6-month period compared to €26,989 in the control group (p=0.825). Furthermore, people with direct oral feeding required significantly less home care assistance; i.e. 23 (48.9%) intervention patients versus 37 (77.1%) control patients (p=0.004). Also, QoL in patients with direct oral feeding progressed more quickly when compared to the control group.

Limitations: Hospital costs were derived from a single hospital unit whereas costs from all the participating units may be a better reflection of the cost deviation. Availability of home care data was limited, leading to difficulty in detecting differences in costs.

Conclusion: This study suggests that direct oral feeding leads to similar total costs and a significantly reduced need for home care assistance. Furthermore, QoL in intervention group increased more quickly when compared to the control group.

6.1. INTRODUCTION

Esophageal cancer is the sixth leading cause of cancer-related mortality and the eighth most common cancer worldwide.[1] The incidence of esophageal cancer in the Netherlands and other Western countries is increasing rapidly.[2-4] In the Netherlands, this is growing at a rate of roughly 400% in the recent years from 684 diagnoses in 1989 to 2,500 in 2018.[5, 6] A total of 2,536 new cases were identified in 2019.[7] This is due to the increasing prevalence of known risk factors such as obesity, gastroesophageal reflux disease and smoking.[8, 9] The Dutch healthcare costs for esophageal cancer care are expected to increase in the future with the increasing incidence and the improved neoadjuvant and surgical treatment.[10] Esophagectomy remains the cornerstone in esophageal cancer treatment. Postoperative complications following an esophagectomy are substantial and associated with a prolonged hospital stay, increased resource use and a reduced quality of life (QoL).[11, 12]

Enhanced recovery after surgery (ERAS) protocols that aim to improve postoperative recovery after an esophagectomy and thereby reducing the cost burden, are more frequently implemented.[13] Although early start of nutrition is an essential part of ERAS, oral intake is often delayed for at least five days in patients undergoing an esophagectomy because of fear of increased complications. Recently it was demonstrated that direct oral feeding was well tolerated and resulted in a similar functional recovery and complication rate compared to standard of care.[14] Patients in the intervention group directly started a oral diet whereas patients in standard of care received nil-by-mouth for the first 5 days after surgery and tube feeding.

The aim of the current study is to assess treatment costs (including need for home care) and QoL in patients that started oral feeding directly following minimally invasive esophagectomy (MIE) compared to patients receiving standard of care.

6.2. METHODS

For this study, we used data of patients participating in the NUTritional Route In Esophageal Resection Trial (NUTRIENT) II study.[14] The NUTRIENT II study was approved by the Medical Ethics Committee United (MEC-U) and registered at ClinicalTrials.gov with the registration number NCT02378948 and at the Dutch trial registry with registration number NTR4972. The NUTRIENT II study was a multicenter prospective open-label randomized controlled trial performed at two hospital units in the Netherlands and one hospital in Sweden between October 1, 2015, and May 14, 2018. The trial was designed to investigate the effects of direct oral feeding versus standard of care on functional recovery following esophagectomy. Inclusion criteria were patients aged 18 or older, undergoing elective minimally invasive esophagectomy for cancer with intrathoracic anastomosis. Exclusion criteria were inability for oral intake (congenital or traumatic anatomical abnormalities), inability to place a feeding jejunostomy, inability to provide written consent, swallowing disorder, achalasia, Karnofsky Performance Status <80 and malnutrition.

Patients in the direct oral feeding group received a liquid/ purified diet directly postoperatively with a daily inclining volume.[14] On postoperative day (POD) 20, a solid diet was started. In these patients a jejunostomy was inserted and used only when oral intake was neither possible nor sufficient. Patients in the control group received tube feeding via jejunostomy and were only allowed sips of water up to 250cc for the first 4 days and then gradually expanded their oral intake similarly to the intervention cohort.

All patients provided written informed consent. Data on hospital costs, home care usage and costs, and health-related QoL of patients were analyzed. Quality of life data was obtained using questionnaires (patient reported) whereas cost data for each patient was obtained using electronic hospital system (i.e. individual data separately recorded for each patient in the clinical trial; patient level). In the original trial, a total of 132 patients were included of which 65 patients in the direct oral feeding group and 67 patients in the standard of care group. In order to adequately analyze the costs in this study, data was only gathered for the Dutch centers (direct oral feeding, n=47 versus control, n=48) Hospital cost analysis, home care usage and cost analysis were based on patients from one hospital and region (the Catharina Hospital from Eindhoven (n=95).

6.2.1. Hospital costs

Hospital costs were determined by retrospectively extracting financial data from the electronic hospital system. Hospital costs were defined as all costs made during the initial admission (i.e. surgery costs and admission costs) as well as readmission and costs at the outpatient clinic. Surgery costs were based on the operating room costs (depicted by the duration of surgery and a fixed starting rate) and operating room personnel costs. Admission costs included costs made for surgical ward and/or intensive care unit stay, charges for parenteral and tube feeding, and postoperative diagnostic procedure. Costs of readmission within 6 months after surgery due to complications related to the primary operation were also collected. Outpatient costs consisted out of costs made for outpatient visits and additional diagnostic procedures within the 6 months after surgery. Monetary units are expressed in Euros (€).

6.2.2. Home care

Routine home care after an esophagectomy consisted of cleaning of the jejunostomy, flushing of the jejunostomy tube and connection of the jejunostomy tube to the feeding pump. Since, tube feeding is the main denominator for patients requiring home care after esophagectomy, data regarding tube feeding, home care assistance and costs for a period of 6 months following surgery were requested from the home care organizations. Patients requiring additional care (rehabilitation including home care) after discharge were scored as needing home care assistance, but excluded from home care cost analysis due to lack of availability of data. Data was gathered from home care organizations regarding the number of days receiving home care and corresponding home care costs. Based on the available home care costs, average costs of home care per day and total costs per patient were calculated. The average home care costs per patient were extrapolated to all patients receiving home care.

6.2.3. Health-related QoL

Health-related QoL was assessed pre- and postoperatively using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire(QLQ)-C30 (version 3.0), a validated questionnaire to measure the QoL in patients with cancer.[15] Additionally, the EORTC QLQ-OG25 supplements the EORTC QLQ-C30 when assessing health-related QoL in patients with esophageal, junctional or gastric cancer. Questionnaires were administrated at baseline (up to two weeks prior to surgery), 6 weeks, 12 weeks and 6 months postoperatively. Missing data were imputed according to the EORTC guidelines.[16]

EORTC QLQ-C30 questionnaire is composed of 5 functional scales (physical, role, social, emotional and functional) and 3 symptom scales (fatigue, nausea/vomiting, and pain) and a global health status/QoL scale. Furthermore, it contains 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The QLQ-OG25 has a functional scale (Body image) and symptom scales (dysphagia, eating, reflux, odynophagia, pain, anxiety, eating with others, dry mouth, trouble with taste and swallowing saliva, choked when swallowing, trouble with coughing, weight loss and hair loss). All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale, represents a high level of functioning, a high score for the global health status represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomology/problems.

6.3. STATISTICAL ANALYSIS

All statistical analyses were performed using IBM SPSS Statistic Version 24 for Windows (IBM corp., Armond, NY, USA). Normally distributed data are presented as mean with standard deviation and tested using an independent T-test. Nonparametric data are presented as median with interquartile range and were tested using the Mann-Whitney U test. All initial analyses were performed using an intention-to-treat approach. Also, a per-protocol analysis on hospital costs was performed to explain the effect of complications after esophagectomy. In short, only patients adhering to any nutritional protocol (i.e. either direct oral feeding or control group) were compared to patients deviating from any nutritional protocol.[14] Cost data were presented as mean, median and 95% confidence interval (CI). Cost differences were checked with nonparametric bootstrapping based on 5,000 replications. Mean and median cost data were compared using the unpaired T-test and Mann-Whitney U test.

6.4. RESULTS

6.4.1. Clinical outcomes

Clinical outcomes of the NUTRIENT study have been previously published.[14] Median age was 65 years, predominantly male with an adenocarcinoma (77/95) of the distal esophagus (58/95). Functional recovery was comparable for both groups (7 in the intervention versus 8 days in the control group). Furthermore, the total postoperative complication rate was similar between groups (43.1% in intervention group versus 50.7% in control group).

6.4.2. Hospital costs

Total mean costs after an esophagectomy were €26,014 in direct oral feeding group and €26,989 in the control group (p=0.825) and mostly determined by initial admission costs; see Table 1 for hospital costs in the 6 months following surgery.

Patients who adhered to any nutritional protocol (i.e. direct oral feeding or standard of care) to patients who deviated from any nutritional protocol, had significantly lower admission (€10,767 versus €30,913; p<0.001), readmission (€2,697 versus € 4,097; p=0.525) and total hospital costs (€19,258 versus €40,777; p<0.001). Surgery (€4,096 versus €4,084; p=0. 914) and outpatient costs (€1,697 versus €1,682; p=0.976) were similar in the intervention and control group.

6.4.3. Home care

Tube feeding at hospital and home was required in 18 out of 47 intervention patients (38.3%) and in all patients receiving the standard of care. The median number of the days patients receiving tube feeding was significantly shorter in the intervention group (0 days [IQR 0-41]) when compared to the control group (28 days [IQR 21-50], p<0.001).

The need for home care assistance was significantly lower in the intervention group; 23 patients (48.9%) compared to 37 patients (77.1%) in the control group (p=0.004). One patient in the intervention group and two patients in the control group required additional care after discharge, thus were excluded from home care cost analysis. Data regarding the length of home care assistance was only available in 32 (53.3%) patients and home care costs were known for 14 (23.3%) patients. Average home care cost was estimated on €37.34 per day and €1,310.31 per patient. Home care costs in the intervention group were estimated €28,826.39 (€1310.31*22) and €45,860.16 (€1310,31*35) in the control group respectively (see Table 2).

Table 1. Hospital cost analysis for a period of 6 months after surgery, comparing the direct oral feeding group with the standard of care group

	Direct oral feeding N=47			Standard of care N=48			p-value	
	Mean	Median	95% CI	Mean	Median	95% CI	T-test	MWU
Admission costs	18,081	11,058	[13,119 - 24,781]	17,035	13,675	[13,730 - 20,790]	0.769	0.457
Surgery costs	4,095	4,059	[3,961 - 4,233]	4,089	3,987	[3,936 - 4,251]	0.961	0.777
Readmission costs	2,156	0	[936 - 3,855]	4,159	0	[1,698 - 7,676]	0.336	0.153
Outpatient costs	1,680	973	[1,069 - 2,573]	1,704	1,101	[1,278 - 2,202]	0.958	0.164
Total costs	26,014	17,182	[20,397 - 32,881]	26,989	20,442	[22,055 - 33,075]	0.825	0.24

All costs are presented in €. CI, confidence interval. MWU, Mann-Whitney U.

Table 2. Tube feeding and home care analysis of patients in the direct oral feeding compared to standard of care group for a period of 6 months after surgery

	Direct oral feeding N=47			Standard of care N=48			P-value	
	N	%	Median [IQR]	N	%	Median [IQR]	Chi^2	MWU
Tube feeding, days	18	38.3	0 [0 - 41]	48	100	28 [21-50]	<0.001	<0.001
Home care assistance, total costs*	23	48.9	28,826.39	37	77.1	45,860.16	0.004	

Costs are presented in €. Chi^2, Chi-square. MWU, Mann-Whitney U. IQR, interquartile range. *One patient in the intervention and two patients in the control group received institutional home care, so data was excluded in the cost analysis: 22 and 35 respectively.

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6.4.4. Health-related QoL

In total, 126 (95%) patients completed the preoperative baseline QoL questionnaire, 110 (83%) patients completed the questionnaire at 6 weeks, 113 (85%) patients at 12 weeks and 100 (75%) patients at 6 months postoperatively. As a result, a total of 118 patients completed the questionnaires at two or more time points (56 patients in the direct oral feeding group and 62 patients in the standard of care group).

QoL in the direct oral feeding increased quicker in time compared with QoL of patients in the control group (see Figure 1). Both groups had a score of 83 at 6 months postoperative. Global QoL score did not significantly differ between the intervention and control group for the 4 perioperative measurements (supplementary Table S1).

Insomnia score at 12 weeks postoperative showed a significantly lower median in the intervention group (p=0.041). At six months postoperative, significantly less patients from the direct oral feeding group experienced diarrhea (p=0.024). Also nausea/ vomiting (p=0.033), odynophagia (p=0.046) and trouble with taste (p=0.028) showed a significant difference while the median scores were similar. No other significant differences were observed between the groups. Complete health-related QoL scores are shown in supplementary Table S1 (QLQ-C30) and supplementary Table S2 (QLQ-OG25).

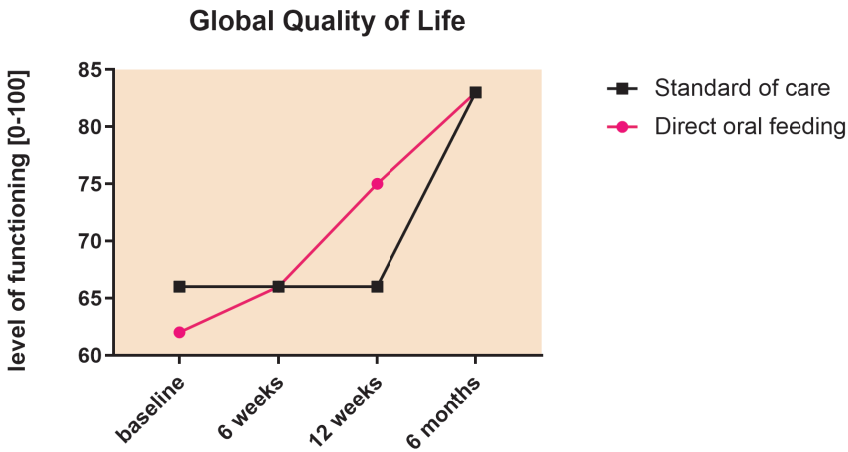

Figure 1. Global quality of life for patients receiving direct oral feeding (intervention) and standard of care (nil-by-mouth for 5 days and tube feeding, control). Baseline measurement was up to 2 weeks prior to surgery. Median with Interquartile range: <u>Baseline</u> direct oral feeding (DOF) 62[50-75], standard of care (SOC) 66[50-75]; <u>6 weeks</u> DOF 66[50-75], SOC 66[50-75]; <u>12 weeks</u> DOF 75[66-83], SOC 66[66-83]; <u>6 months</u> DOF 83[75-83], SOC 83[66-83].

6.5. DISCUSSION

This study suggests that patients starting with oral intake directly following esophagectomy had lower home care costs and progressed more quickly to a higher QoL than patients with nil-by-mouth for five days and tube feeding. Also, it was shown that total costs following esophagectomy are high and mainly determined by initial admission period and admission related costs.

To our knowledge, no other studies have compared direct oral feeding with tube feeding and nil-by-mouth directly after (minimally invasive) esophagectomy in terms of costs and quality of life. In the current trial, all patients were operated upon with a minimally invasive approach. Previous studies comparing MIE with open surgery have shown increased surgical costs, but lower postoperative costs in the MIE group, resulting in conflicting conclusions. Total costs[17] and surgical costs[11, 18] for MIE in the current trial were lower than the costs for the open or combined open and minimally invasive approach in other studies. Differences between studies could be explained by effective implementation of an ERAS protocol leading to an optimized postoperative care pathway and an acceptable complication rate that is reduced following a learning curve.[13, 18-20] Compared to the current results, Weindelmayer *et al* – only including open Ivor Lewis esophagectomies – found higher surgical costs (in contrast with previous studies stating surgical costs are higher in the MIE setting[17]) while admission costs were lower. Hospital costs in this study were slightly lower compared to a randomized trial by Hulscher *et al* of adenocarcinoma patients undergoing an open esophagectomy between 1994 and 2000.[21] A more recent study by Goense *et al*, found average hospital costs of €37,571 from esophagectomy until 90 days after discharge. This is higher than in the current trial, in which the study period includes hospital costs from esophagectomy until 6 months postoperative.[11] In multivariable analysis they found an increase in costs for female patients, age >70 year and several postoperative complications (anastomotic leakage, cardiac complications, chyle leakage and postoperative bleeding). Since the cohort of Goense *et al* consisted of more female patients with a higher age, and both the AL and chyle leakage rates were 10% higher, this could explain the difference found between studies. Noteworthy, the significantly reduced chyle leakage rate found in the direct oral feeding group of NUTRIENT II trial[14] and the succeeding analysis[22] implies direct oral feeding could further reduce costs in these patients. Importantly, the learning curve was surpassed, thereby reducing the complication rate and complication-related costs.

In line, hospital costs for patients deviating from their nutritional protocol – which can be regarded as a proxy for a (severely) complicated postoperative course[14] – were significantly higher compared to patients abiding to their nutritional protocol in this study. This was despite the presence of (minor) complications not prohibiting intake according to protocol.

The current standard of care is tube feeding via jejunostomy to ensure sufficient intake after esophagectomy. However, weight loss following esophagectomy occurs once tube feeding is stopped[23] regardless of the postoperative feeding regimen (oral vs. enteral)[24]. Moreover, the need for prolonged routine feeding jejunostomy for enteral nutrition is being questioned[25-27] due to the frequent occurrence of jejunostomy-related complications[23, 27], For example, bowel obstruction which is a severe jejunostomy-related complication has been found to be significantly higher in patients that received enteral feeding via a jejunostomy.[25, 28] Furthermore, a randomized pilot study for 6 weeks home enteral nutrition found no clear cost-effectiveness of prolonged enteral feeding.[29]

In this study, total home care costs were based on data obtained for a smaller cohort and extrapolated to all patients needing home care assistance. Retrieval of home care data was challenging due privacy guidelines of home care facilities to share data, which resulted in the need for additional consent from all patients that participated in the trial. Despite the lack of a formal trial-based economic evaluation, the higher amount of patients receiving tube feeding and the longer period of tube feeding in the control group implies that this relative cost-effectiveness in absolute cost might be different, but always indicate superiority of the intervention group.

Hospital and home care cost analyses in this study imply that routine implementation of direct oral feeding after surgery could lead to a substantial reduction of costs and patient burden of home care organizations without compromising long-term outcomes on weight and even improving QoL.

QoL persistently improved after surgery in the direct oral feeding group whereas this improvement was not observed until six months after surgery in the control group. A possible explanation for this phenomenon could be that patients received tube feeding for a shorter period, or not at all. To our knowledge, only one other trial studying QoL in patients with early oral feeding after upper GI surgery by Sun *et al* reported a significantly improved global QoL for patients with early oral feeding after a McKeown esophagectomy.[30] Two reasons could explain the difference with the current study: [1] patients in the control group received a naso-enteral feeding tube on POD 1, potentially leading to a diminished QoL caused by the discomfort of these feeding tubes which were not inserted in the intervention group, and [2] the first (global) QoL measurement was at 2 weeks postoperative. The significantly higher global QoL found by Sun *et al* at 2 and 4 weeks postoperative equalized between their intervention and control group at 8 weeks postoperative, and since the 8 weeks values are comparable with the global QoL found in the current study, this suggests our measurement of QoL at 6 weeks postoperative was too late to find a significant difference.

When comparing global QoL with other studies, the population in this study performed better at 6 months postoperative. Kauppila *et al* showed a global QoL score of 63 (95% CI 57-69) at 6 months postoperative.[31] Akkerman *et al* studied patients alive without disease recurrence at 1 year or more after surgery (median 36 months, range 12-75) and found a global QoL comparable with their used Dutch background population (mean 76 [SD 19] vs. mean 78 [SD 17])[32], but lower than the population at final study follow-up in this study. In disease-free patients, QoL is expected to restore within 6 months after surgery.[33] The expectation is that the QoL in this cohort would further improve over time, since symptoms like fatigue, pain and coughing problems can persist for at least a year after surgery.[34]

Few symptoms were significantly different at long-term follow-up. Nausea/ vomiting and diarrhea at 6 months in the current trial were comparable with Kauppila *et al*.[31] Diarrhea at 6 months in the intervention group was already comparable with the symptom level of patients at 36m after surgery measured by Akkerman *et al*.[31, 33]

An important strength of this study was that patient level data was collected as a part of randomized controlled trial. However, this study also has some limitations. First, hospital costs were derived from a single hospital unit whereas costs from all the participating units may be a better reflection of the cost deviation. Second, limited availability of home care data which leads to difficulty to detecting differences in the costs. Lastly, the study was conducted based on a single center data which may limit the generalizability of the results.[35] Further studies with a full economic evaluation comparing costs from a societal or health insurance perspective and using QALY as outcome would be needed to confirm the cost-effectiveness of the intervention.

In conclusion, implementation of direct start of oral feeding lead to a significant reduction of patients requiring home care assistance and related costs, and a quicker increase in quality of life while hospital costs were similar between groups. Since direct start of oral feeding resulted in a similar postoperative complication rate in multicenter international setting and significantly reduced complications in a center with a stable and acceptable postoperative complication rate, it may also reduce costs after adopting of a safe and feasible direct oral feeding protocol.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
2. Fransen LFC, Berkelmans GHK, Asti E, van Berge Henegouwen MI, Berlth F, Bonavina L, et al. The Effect of Postoperative Complications After Minimally Invasive Esophagectomy on Long-term Survival: An International Multicenter Cohort Study. Annals of surgery. 2020.
3. van der Werf LR, Busweiler LAD, van Sandick JW, van Berge Henegouwen MI, Wijnhoven BPL. Reporting National Outcomes After Esophagectomy and Gastrectomy According to the Esophageal Complications Consensus Group (ECCG). Annals of surgery. 2020;271(6):1095-101.
4. Markar SR, Ni M, Gisbertz SS, van der Werf L, Straatman J, van der Peet D, et al. Implementation of Minimally Invasive Esophagectomy From a Randomized Controlled Trial Setting to National Practice. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2020;38(19):2130-9.
5. IKNL. 2019 [cited 28/07/2020]. Available from: https://www.iknl.nl/nieuws/2019/laatste-incidentiecijfers-voor-slokdarm-,-maag-en.
6. Dikken JL, Lemmens VE, Wouters MW, Wijnhoven BP, Siersema PD, Nieuwenhuijzen GA, et al. Increased incidence and survival for oesophageal cancer but not for gastric cardia cancer in the Netherlands. European journal of cancer (Oxford, England : 1990). 2012;48(11):1624-32.
7. Incidentie slokdarmkanker [Internet]. KWF. 2020 [cited 28/07/2020]. Available from: https://www.kwf.nl/kanker/kwf-en-slokdarmkanker/Pages/default.aspx.
8. Domper Arnal MJ, Ferrández Arenas Á, Lanas Arbeloa Á. Esophageal cancer: Risk factors, screening and endoscopic treatment in Western and Eastern countries. World J Gastroenterol. 2015;21(26):7933-43.
9. Huang FL, Yu SJ. Esophageal cancer: Risk factors, genetic association, and treatment. Asian journal of surgery. 2018;41(3):210-5.
10. Slobbe LCJ SJ, Groen J, Poos M.J.J.C KG. Kosten van ziekten in Nederland 2007: Trends in de Nederlandse zorguitgaven 1999-2010. RIVM Rapp 270751023. 2011;28-12-2011. 2008.
11. Goense L, van Dijk WA, Govaert JA, van Rossum PS, Ruurda JP, van Hillegersberg R. Hospital costs of complications after esophagectomy for cancer. Eur J Surg Oncol. 2017;43(4):696-702.
12. Carrott PW, Markar SR, Kuppusamy MK, Traverso LW, Low DE. Accordion severity grading system: assessment of relationship between costs, length of hospital stay, and survival in patients with complications after esophagectomy for cancer. Journal of the American College of Surgeons. 2012;215(3):331-6.
13. Shewale JB, Correa AM, Baker CM, Villafane-Ferriol N, Hofstetter WL, Jordan VS, et al. Impact of a Fast-track Esophagectomy Protocol on Esophageal Cancer Patient Outcomes and Hospital Charges. Annals of surgery. 2015;261(6):1114-23.
14. Berkelmans GHK, Fransen LFC, Dolmans-Zwartjes ACP, Kouwenhoven EA, van Det MJ, Nilsson M, et al. Direct Oral Feeding Following Minimally Invasive Esophagectomy (NUTRIENT II trial): An International, Multicenter, Open-label Randomized Controlled Trial. Annals of surgery. 2020;271(1):41-7.

15. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. JNCI: Journal of the National Cancer Institute. 1993;85(5):365-76.
16. Fayers P, Bottomley A. Quality of life research within the EORTC—the EORTC QLQ-C30. European Journal of Cancer. 2002;38:125-33.
17. Liu CY, Lin CS, Shih CS, Huang YA, Liu CC, Cheng CT. Cost-Effectiveness of Minimally Invasive Esophagectomy for Esophageal Squamous Cell Carcinoma. World J Surg. 2018;42(8):2522-9.
18. Weindelmayer J, Verlato G, Alberti L, Poli R, Priolo S, Bovo C, et al. Enhanced recovery protocol in esophagectomy, is it really worth it? A cost analysis related to team experience and protocol compliance. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus. 2019;32(8).
19. van Workum F, Fransen L, Luyer MD, Rosman C. Learning curves in minimally invasive esophagectomy. World J Gastroenterol. 2018;24(44):4974-8.
20. van Workum F, Stenstra M, Berkelmans GHK, Slaman AE, van Berge Henegouwen MI, Gisbertz SS, et al. Learning Curve and Associated Morbidity of Minimally Invasive Esophagectomy: A Retrospective Multicenter Study. Annals of surgery. 2019;269(1):88-94.
21. Hulscher JB, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. The New England journal of medicine. 2002;347(21):1662-9.
22. Fransen LFC, Janssen T, Aarnoudse M, Nieuwenhuijzen GAP, Luyer MDP. Direct Oral Feeding After a Minimally Invasive Esophagectomy: A Single-Center Prospective Cohort Study. Annals of surgery. 2020.
23. Weijs TJ, van Eden HWJ, Ruurda JP, Luyer MDP, Steenhagen E, Nieuwenhuijzen GAP, et al. Routine jejunostomy tube feeding following esophagectomy. Journal of thoracic disease. 2017;9(Suppl 8):S851-s60.
24. Berkelmans GHK, Fransen L, Weijs TJ, Lubbers M, Nieuwenhuijzen GAP, Ruurda JP, et al. The long-term effects of early oral feeding following minimal invasive esophagectomy. Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus. 2018;31(1):1-8.
25. Akiyama Y, Iwaya T, Endo F, Nikai H, Sato K, Baba S, et al. Evaluation of the need for routine feeding jejunostomy for enteral nutrition after esophagectomy. Journal of thoracic disease. 2018;10(12):6854-62.
26. Luyer MDP. Tube feeding via a jejunostomy following esophagectomy: is it necessary? Journal of thoracic disease. 2019;11(3):621-3.
27. Álvarez-Sarrado E, Mingol Navarro F, R JR, Ballester Pla N, Vaqué Urbaneja FJ, Muniesa Gallardo C, et al. Feeding Jejunostomy after esophagectomy cannot be routinely recommended. Analysis of nutritional benefits and catheter-related complications. American journal of surgery. 2019;217(1):114-20.
28. Tao Z, Zhang Y, Zhu S, Ni Z, You Q, Sun X, et al. A Prospective Randomized Trial Comparing Jejunostomy and Nasogastric Feeding in Minimally Invasive McKeown Esophagectomy. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract. 2019.

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29. Bowrey DJ, Baker M, Halliday V, Thomas AL, Pulikottil-Jacob R, Smith K, et al. A randomised controlled trial of six weeks of home enteral nutrition versus standard care after oesophagectomy or total gastrectomy for cancer: report on a pilot and feasibility study. Trials. 2015;16:531.
30. Sun HB, Li Y, Liu XB, Zhang RX, Wang ZF, Lerut T, et al. Early Oral Feeding Following McKeown Minimally Invasive Esophagectomy: An Open-label, Randomized, Controlled, Noninferiority Trial. Annals of surgery. 2018;267(3):435-42.
31. Kauppila JH, Ringborg C, Johar A, Lagergren J, Lagergren P. Health-related quality of life after gastrectomy, esophagectomy, and combined esophagogastrectomy for gastroesophageal junction adenocarcinoma. Gastric cancer : official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association. 2018;21(3):533-41.
32. Akkerman RD, Haverkamp L, van Rossum PS, van Hillegersberg R, Ruurda JP. Long-term quality of life after oesophagectomy with gastric conduit interposition for cancer. European journal of cancer (Oxford, England : 1990). 2015;51(12):1538-45.
33. Zieren HU, Jacobi CA, Zieren J, Muller JM. Quality of life following resection of oesophageal carcinoma. Br J Surg. 1996;83(12):1772-5.
34. Jacobs M, Macefield RC, Elbers RG, Sitnikova K, Korfage IJ, Smets EM, et al. Meta-analysis shows clinically relevant and long-lasting deterioration in health-related quality of life after esophageal cancer surgery. Qual Life Res. 2014;23(4):1097-115.
35. Drummond M, Manca A, Sculpher M. Increasing the generalizability of economic evaluations: recommendations for the design, analysis, and reporting of studies. International journal of technology assessment in health care. 2005;21(2):165-71.

SUPPLEMENTARY INFORMATION

Table S1: Health-related quality of life scores for a total of 118 patients, assessed by the EORTC QLQ-C30

Dimension	**Baseline**			**Postoperative 6 weeks**			**Postoperative 12 weeks**			**Postoperative 6 months**		
	Direct oral feeding N=56	Standard of care N=62	P-value	Direct oral feeding N=56	Standard of care N=62	P-value	Direct oral feeding N=56	Standard of care N=62	P-value	Direct oral feeding N=56	Standard of care N=62	P-value
Global quality of life	62 [50 - 75]	66 [50 - 75]	0.886	66 [50 - 75]	66 [50 - 75]	0.886	75 [66 - 83]	66 [66 - 83]	0.171	83 [75 - 83]	83 [66 - 83]	0.416
Functional scales*												
Physical functioning	80 [66 - 86]	80 [66 - 86]	0.626	80 [66 - 86]	80 [66 - 86]	0.663	86 [80 - 93]	86 [80 - 93]	0.996	86 [81 - 98]	86 [86 - 93]	0.501
Role functioning	58 ± 27	56 ± 30	0.686	58 ± 27	56 ± 30	0.686	70 ± 25	68 ± 28	0.652	75 [66 - 100]	66 [66 - 100]	0.9
Emotional functioning	91 [75 - 100]	91 [66 - 100]	0.754	83 [75 - 100]	83 [66 - 100]	0.681	91 [83 - 100]	91 [83 - 100]	0.71	91 [83 - 100]	91 [81 - 100]	0.91
Cognitive functioning	91 [83 - 100]	83 [66 - 100]	0.286	85 ± 16	81 ± 19	0.204	100 [83 - 100]	100 [83 - 100	0.098	83 [83 - 100]	83 [66 - 100]	0.774
Social functioning	72 ± 23	72 ± 21	0.951	73 ± 23	74 ± 21	0.877	100 [83 - 100]	83 [66 - 100]	0.141	100 [83 - 100]	100 [83 - 100]	0.552
General symptom scales**												
Fatigue	42 ± 21	40 ± 24	0.578	42 ± 21	39 ± 23	0.527	33 [11 - 33]	33 [19 - 44]	0.309	33 [11 - 33]	33 [11 - 33]	0.814
Nausea/vomiting	16 [0 - 33]	18 [0 - 33]	0.547	16 [0 - 16]	16 [0 - 33]	0.446	8 [0 - 16]	0 [0 - 16]	0.748	16 [0 - 16]	16 [0 - 33]	**0.033**
Pain	16 [0 - 29]	16 [0 - 33]	0.374	16 [0 - 29]	16 [0 - 33]	0.374	0 [0 - 16]	0 [0 - 16]	0.826	0 [0 - 0]	0 [0 - 16]	0.565
Dyspnea	30 ± 28	30 ± 26	0.868	30 ± 28	30 ± 26	0.868	23 ± 24	25 ± 26	0.661	0 [0 - 33]	0 [0 - 33]	0.501
Insomnia	31 ± 32	33 ± 31	0.765	31 ± 32	33 ± 31	0.765	0 [0 - 33]	33 [0 - 33]	**0.041**	0 [0 - 33]	16 [0 - 33]	0.536
Appetite loss	36 ± 30	41 ± 32	0.387	36 ± 30	41 ± 32	0.387	0 [0 - 33]	33 [0 - 33]	0.647	19 ± 20	27±29	0.079
Constipation	0 [0 - 33]	0 [0 - 33]	0.622	0 [0 - 33]	0 [0 - 33]	0.622	0 [0 - 0]	0 [0 - 0]	0.592	0 [0 - 0]	0 [0 - 0]	0.349
Diarrhea	0 [0 - 33]	0 [0 - 33]	0.491	26 ± 28	23 ± 24	0.456	0 [0 - 33]	33 [0 - 33]	0.372	15 ± 17	25 ± 29	**0.024**
Financial problems	0 [0 - 0]	0 [0 - 0]	0.772	0 [0 - 0]	0 [0 - 0]	0.772	0 [0 - 0]	0 [0 - 0]	0.644	0 [0 - 0]	0 [0 - 0]	0.085

Values are mean ± standard deviation or median [interquartile range]. EORTC, European Organization for Research and Treatment of Cancer. QLQ, Quality of Life Questionnaire. * Higher value represents higher functioning level. ** Higher value represents more severe symptoms.

Table S2: Health-related quality of life scores for a total of 118 patients, assessed by the EORTC QLQ-OG25

Dimension	Baseline			Postoperative 6 weeks			Postoperative 12 weeks			Postoperative 6 months		
	Direct oral feeding N=56	Standard of care N=62	P-value	Direct oral feeding N=56	Standard of care N=62	P-value	Direct oral feeding N=56	Standard of care N=62	P-value	Direct oral feeding N=56	Standard of care N=62	P-value
Body image	100 [66 - 100]	100 [100 - 100]	0.123	100 [66 - 100]	100 [100 - 100]	0.123	100 [100 - 100]	100 [100 - 100]	0.69	100 [100 - 100]	100 [100 - 100]	0.335
Dysphagia	11 [0 - 22]	11 [0 - 33]	0.262	11 [0 - 22]	11 [0 - 33]	0.262	11 [0 - 11]	11 [0 - 22]	0.065	11 [0 - 11]	11 [0 - 13]	0.236
Eating	38 ± 25	42 ± 26	0.33	38 ± 25	42 ± 26	0.33	26 ± 19	32 ± 22	0.093	25 [8 - 33]	33 [14 - 41]	0.159
Reflux	0 [0 - 33]	0 [0 - 33]	0.79	0 [0 - 33]	0 [0 - 33]	0.79	0 [0 - 33]	0 [0 - 33]	0.663	16 [0 - 16]	16 [0 - 33]	0.485
Odynophagia	8 [0 - 16]	16 [0 - 16]	0.312	8 [0 - 16]	16 [0 - 16]	0.312	0 [0 - 16]	0 [0 - 16]	0.378	0 [0 - 12]	0 [0 - 16]	**0.046**
Pain and discomfort	13 ± 14	19 ± 21	0.101	13 ± 14	19 ± 21	0.101	0 [0 - 29]	0 [0 - 33]	0.252	0 [0 - 16]	0 [0 - 33]	0.679
Anxiety	33 [0 - 33]	33 [16 - 50]	0.338	33 [0 - 33]	33 [16 - 50]	0.338	33 [0 - 33]	33 [0 - 33]	0.715	33 [0 - 33]	33 [0 - 33]	0.434
Eating with others	0 [0 - 0]	0 [0 - 0]	0.63	0 [0 - 0]	0 [0 - 0]	0.63	0 [0 - 0]	0 [0 - 0]	0.754	0 [0 - 0]	0 [0 - 0]	0.423
Dry mouth	28 ± 28	24 ± 27	0.396	28 ± 28	24 ± 27	0.396	0 [0 - 33]	16 [0 - 33]	0.31	0 [0 - 33]	0 [0 - 33]	0.773
Trouble with taste	25 ± 29	30 ± 29	0.302	25 ± 29	30 ± 29	0.302	0 [0 - 33]	33 [0 - 33]	0.128	0 [0 - 0]	0 [0 - 33]	**0.028**
Trouble swallowing saliva	0 [0 - 0]	0 [0 - 0]	0.69	0 [0 - 0]	0 [0 - 0]	0.69	0 [0 - 0]	0 [0 - 0]	0.816	0 [0 - 0]	0 [0 - 0]	0.687
Choked when swallowing	0 [0 - 0]	0 [0 - 0]	0.873	0 [0 - 0]	0 [0 - 0]	0.873	0 [0 - 0]	0 [0 - 33]	0.507	0 [0 - 0]	0 [0 - 0]	0.782
Trouble with coughing	42 ± 25	45 ± 27	0.563	42 ± 25	45 ± 27	0.563	38 ± 26	38 ± 27	0.901	26 ± 19	30 ± 21	0.307
Trouble with talking	0 [0 - 33]	0 [0 - 33]	0.597	0 [0 - 33]	0 [0 - 33]	0.597	0 [0 - 0]	0 [0 - 0]	0.97	0 [0 - 0]	0 [0 - 0]	0.096
Weight loss	29 ± 26	22 ± 25	0.138	29 ± 26	22 ± 26	0.138	33 [0 - 33]	0 [0 - 33]	0.365	33 [0 - 33]	33 [0 - 33]	0.938
Hair loss	33 [0 - 66]	0 [0 - 33]	0.268	33 [0 - 66]	18 [0 - 33]	0.268	33 [0 - 66]	22 [0 - 33]	0.824	40 [0 - 66]	18 [0 - 33]	0.315

Values are mean ± standard deviation or median [interquartile range]. EORTC, European Organization for Research and Treatment of Cancer. QLQ, Quality of Life Questionnaire.

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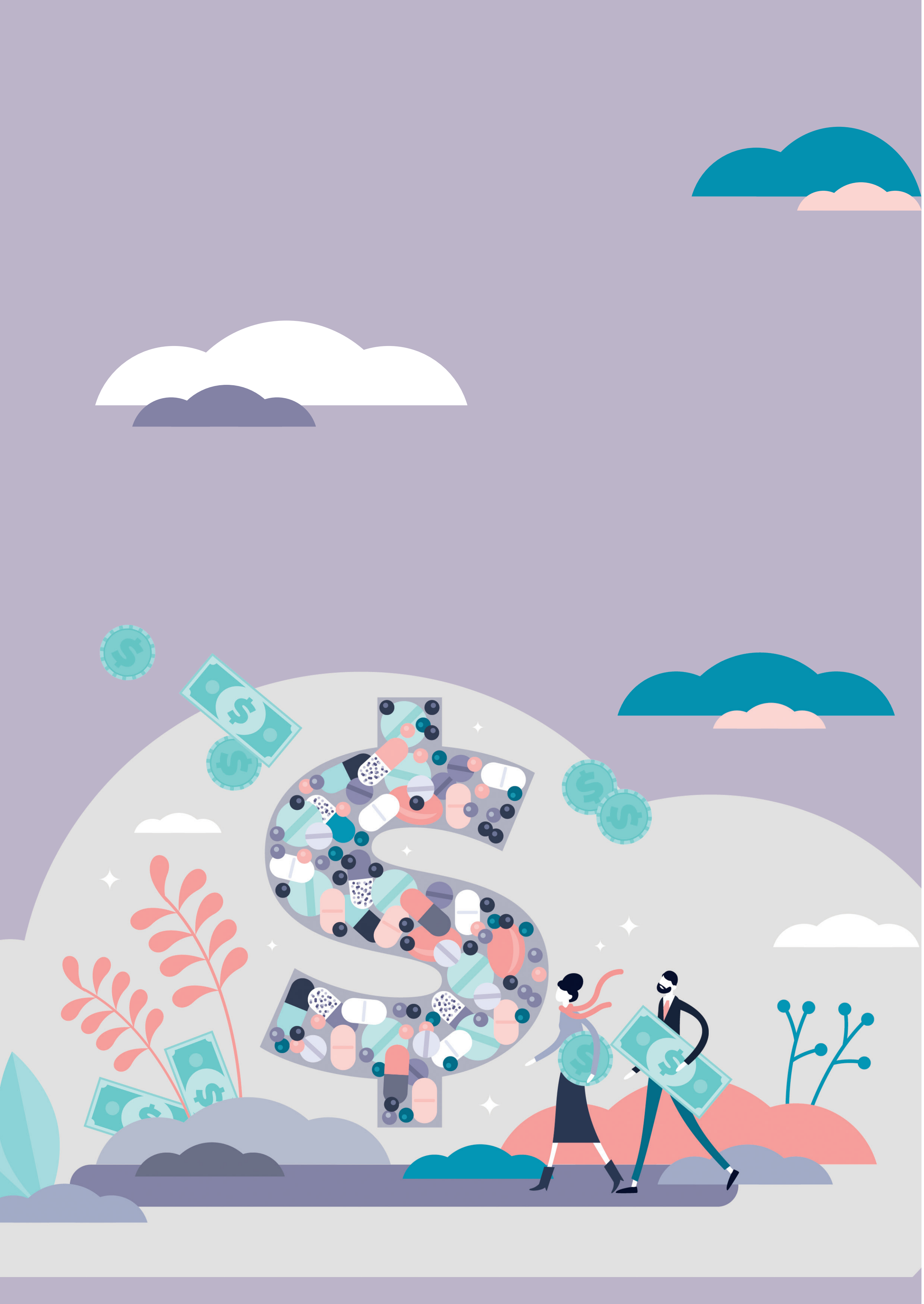


CHAPTER 7

General discussion

The need for evidence-informed decision making in healthcare is becoming increasingly stronger as seen in the decision making process of new interventions to improve the recovery after colorectal and esophageal surgery. New developments in interventions might contribute to rising healthcare costs and compete for resources. Various new interventions that aim to reduce postoperative complications after colorectal and esophageal surgery are currently investigated. This dissertation focussed on nutritional interventions in colorectal cancer (CRC) and esophageal cancer (EC) patients.[1, 2] Nutritional support in these trials vary from oral or enteral nutrition few hours before and after surgery to direct intake after surgery with or without nasogastric tubes inserted in patients. These are relatively low cost interventions with potential large effects, but limited economic data is available for the effect on healthcare expenditures in these patients.[3, 4]

The aim of this dissertation was therefore to assess the cost-effectiveness of these interventions using data gathered in recent randomized controlled trials (RCT). In addition, we also aimed to estimate the burden of CRC and EC to understand the economic and quality of life implications on the patient and society. Burden of illness studies also support economic evaluations and provide important information for future economic analyses of new interventions. Next, a total of three trial-based economic evaluations with nutritional interventions were conducted with the aim to study their effects on postoperative complications, costs and quality of life.

More specifically, in part I of the dissertation, the magnitude of preoperative burden, specifically the costs and quality of life of CRC was assessed (**chapter 2**); next, the burden of postoperative complications of CRC was investigated including how postoperative ileus (POI) increase the inflammation, costs and quality of life (**chapter 3**). In part II, the results of three trial-based economic evaluations (**chapters 4, 5, 6**) evaluated the cost-effectiveness of these new nutritional interventions (i.e. gum chewing in SANICS I trial, perioperative enteral nutrition in SANICS II trial and early oral feeding in NUTRIENT II trial) compared with standard care from a societal perspective.

This final chapter provides a summary of the main findings of this dissertation, discusses the methodological challenges and suggests implications for public health and policy making, as well as research recommendations on new nutritional interventions in CRC and EC.

7.1. Summary of main findings

Part 1 of this dissertation presented two studies conducted to understand the clinical and economic burden of CRC and its complications. Both studies were embedded in an international multicenter RCT (SANICS II). Patients from Dutch hospitals participating in the trial were the basis for estimating the preoperative burden of CRC in the Netherlands. For estimating the burden of complication (POI), all the patients included in the original trial were studied to assess its influence on recovery, costs and quality of life. Costs and quality of life were assessed using the patient-reported questionnaires administered at specific time points during the trial process.

A retrospective cost of illness study **(chapter 2)** was conducted using a bottom-up prevalence based approach. It showed that the mean societal cost per CRC patient was estimated at €3,211 in the 3 months prior to surgery and the utility score of patient prior to surgery derived from EQ-5D was 0.88. Lack of prior research studies from the Netherlands on this topic led to inability to compare the results. However, when the results were compared with some international studies, the utility score was somewhat higher.[5, 6] Comparison of the costs with previous international studies was hampered due to variation in valuing methodology and time period of estimation of costs.[7-9]

Then, the consequences of POI on recovery, costs and quality of life **(chapter 3)** were estimated. Clinical and economic outcomes were compared between patients with and without POI, and in particular patients with POI as a unique complication. Inflammatory parameters (C-reactive Protein levels) were increased in patients with POI compared to patients without POI. The results of this study regarding the rise of inflammatory markers in the blood following surgery are in agreement with a previous study by Boersema[10] and other animal studies as discussed in **chapter 3**. Mean societal costs per patient with POI in this study were 38-47% higher at 3 months postoperatively similar to previous studies.[11-13]. Furthermore this study demonstrated that patients with POI have a higher chance of developing other complications and accompanied 9% increase in costs. Median utility scores were lower in the POI group at both 3 months (0.85 versus 0.89; p=0.023) and 6 months (0.84 versus 0.89; p=0.017) demonstrating a long term burden of POI on patients.

In Part II of the dissertation, three economic studies were conducted to identify if nutritional interventions were cost effective (**chapters 4, 5, 6**). Chapters 4 and 5 are embedded in the SANICS I and SANICS II trials respectively which are based on the hypothesis that nutritional interventions inhibit the vagus nerve and reduce postoperative complications.

Gum chewing as an intervention was first introduced in a pilot clinical study (SANICS I) and the clinical results were positive showing advantages over the placebo group. Gum chewing significantly reduced POI (14/52 patients versus 29/60 patients) and anastomotic leakage (AL) (2/52 patients versus 8/60 patients) compared to placebo. However, the results of our trial-based economic evaluations alongside SANICS I were not conclusive about the economic value of gum chewing. No significant differences in overall hospital costs between groups were observed, however lower costs for ward stay were seen in the gum chewing group. Cost-effectiveness analysis resulted in ICERs expressed in costs per POI or AL. More than 50% of bootstrapped replications for both AL and POI indicated gum chewing was dominant. There were however some major limitations in data availability, potentially limiting the conclusion of the study. For example, utilities were mapped from the QLQ-C30 questionnaires and it was not possible to estimate quality-adjusted life years due to non-standardization of the time point of administration of the questionnaires. There was also a significant number of missing quality of life questionnaires and therefore the results were based on a limited sample size (**chapter 4**). Postoperative gum chewing was not cost effective in a previous study when compared with standard care[14] however, comparing the results of the current study with previous studies is complex due to variations in the timing of the gum chewing, clinical and economic outcomes and perspective of the cost calculation.[14]

A more comprehensive trial-based economic evaluation with the perioperative enteral nutrition (PEN) as the intervention was then conducted. This study included various questionnaires to collect cost and quality of life resources (**chapter 5**) during the trial horizon at baseline, 3 months and 6 months. Although the intervention was similar to SANICS I, the trial did not yield positive clinical results. Lack of clinical effect of PEN on postoperative complications in the trial could be due to various reasons such as adherence to ERAS protocols and inclusion of patients operated via laparoscopy. Nevertheless, we investigated the impact of the intervention on the costs and health-related quality of life and found no significant differences in societal costs (€14,673 versus €11,974; p=0.109) and global quality of life (83 versus 83; p=0.357). The gain in QALY was marginal (0.003) with an additional cost of €2,941 and the ICUR (incremental cost utility ratio) was estimated at €980,333. A previous study with nutritional prehabilitation indicated lower costs and length of hospital stay when compared to the current study however, differences in the control group, route of nutrition and length of perioperative nutritional period were observed and could also explain the difference.[4]

Finally, a third trial to study the postoperative recovery in EC patients with early oral feeding as the intervention was conducted (**chapter 6**). This trial demonstrated that direct oral feeding was well tolerated and resulted in a similar functional recovery and complication rate compared to standard of care. Mean hospital costs were similar between the groups (€26,014 in intervention versus €26,989 in control groups) which was lower when compared to previous studies.[15, 16] The hospital costs in patients deviating from the nutritional protocol were significantly higher when compared with patients that did not deviate from the protocol. Furthermore, it was observed that direct oral feeding significantly reduced the need for home care assistance (48.9% versus 77.1%, p=0.004) and the quality of life increased quicker when compared to control group. QoL in a previous study reported an improvement in patients with early oral feeding as discussed in **chapter 6**.[3]

7.2. METHODOLOGICAL CONSIDERATIONS

Two important methods, namely the cost of illness study and trial-based economic evaluation, were used in this dissertation. This section addresses the methodologic challenges, strengths and limitations of these methods.

7.2.1. Cost of illness studies

Cost of illness studies are being conducted with the aim of highlighting the burden of the disease besides the usual epidemiological estimates such as incidence, prevalence, mortality or morbidity helping determine research priorities and providing baseline against which new interventions can be assessed.[17, 18]

7.2.2. Trial-based economic evaluations

Economic evaluations that compare the costs and outcomes of new interventions with a control intervention are used to inform decision makers on the efficient use of available resources. Trial-based economic evaluations area primary source of data on the cost-effectiveness of health technologies and they are used in health service decision making.

While we aimed to follow available recommendations for conducting cost of illness studies and economic evaluations, conduct of the studies faced some methodological challenges.

A first limitation is the lack of a standard methodology for extracting the primary patient data (resource use, unit costs and home care costs). Data on costs are difficult to obtain since hospitals do not isolate all costs, for example, home care costs. Considering privacy guidelines, all the patients that participated in the trial needed to be consented separately for any home care services that were used and mostly, this has to be done retrospectively. Additionally, it was difficult to obtain the consent from all the home care organizations as not all of them were familiar with the data retrieval process, moreover a large part of data was not being electronically maintained. (**chapter 6**). Furthermore, care organizations have separate and non-transparent agreements with healthcare insurance companies which makes this process of data retrieval tedious and extremely time consuming. Standardization of data gathering and agreement between care organizations and insurance companies for an uncomplicated data retrieval is necessary. Formulating an explicit protocol on methods for home care data extraction in cost studies as well as developing an e-health identifier for easy patient data retrieval would be favourable. Thus, we appeal for effective data sharing options to help achieve swift data acquisition in such studies. Adapting the regulations involving primary and economic patient information in clinical practice can be another solution, however this may give rise to ethical concerns.

The next challenge concerns using the Dutch costing manual that provides guidance to researchers to perform and evaluate economic evaluations in the Netherlands.[19] The manual constitutes reference prices for commonly used healthcare consumption i.e. average unit costs. We, however, noticed that reference prices for some diagnostic procedures and therapies, for instance, MRI abdomen, dialysis, and radiotherapy, etc., within the healthcare sector were missing. Therefore, cost estimation for such procedures was complicated. We, therefore plea to introduce more items in the manual that would benefit researchers working on economic evaluations of various therapies. Relying on hospital tariffs and applying the tariff for these procedures can be a potential alternative.

Another important challenge is the use of nutrition as an intervention in our studies. [20] A systematic approach or specific methodology to assess the impact of nutrition on health and health-related quality of life does not exist. Furthermore, it has been argued that nutritional interventions differ from the routine drug interventions as these are not completely stand-alone and an adjuvant to the medical treatment and have an interdependent nature. It is thus challenging to demonstrate the cause-effect relationship between medical nutrition and overall outcomes. [20] The sensitivity of quality of life instruments such as EQ-5D questionnaire could however be questioned.[21] Although the economic studies in this thesis were based on RCTs with a single independent factor, assessing the cost-effectiveness of medical nutrition is a new area within health economics. Performing economic analysis of such nutritional interventions with basic methodology developed for pharmaceutical products is likely to be inaccurate due to key issues concerning the study design, population and sample size. [20]

New guidelines with a systematic approach in the field of medical nutrition outcomes research are being developed for better performance and judgement of medical nutrition outcomes research .[20, 22] This can be done by appropriate guidance from nutritional specialists, epidemiologists and health technology assessment (HTA) experts.

Missing data and lack of standardization of administration of questionnaires further limited the results of some trial-based economic evaluation (**chapter 4**). A significant amount of data was missing and imputations were made to compensate for this, however, this may have compromised the validity of the trial results. Efforts to increase response rate is important. Optimization of handling of missing data during the planning stage of an RCT[23], engaging the patients by inviting them to make self-reports of health needs, providing feedback of their progress and helping them perceive that their reports will actually serve a purpose[23, 24] are a few methods to improve the response rates. Additionally, utility scores found in our studies were relatively high and assessing if the values are clinically meaningful was not possible without a proper comparison with general Dutch population. Utilities were derived from the Dutch tariff for EQ-5D-5L which could differ from the tariff from other countries. Utility values for general Dutch population are not known and it would be interesting to find such a comparison in the future.

Efforts to increase the validity of the trials are needed. So, we recommend the inclusion of cost and quality of life questionnaires (EQ-5D) at several time points to compare the change in quality of life outcome from baseline to various postoperative time points.

7.3. Implications for decision making, clinical practice and further research recommendations

The results of the cost-effectiveness studies presented in this thesis were inconclusive with no significant differences in costs and quality of life. SANICS I study was further difficult to interpret due to limitations in the data.

Decision making

CRC and EC have been identified as a major public health problem in the Netherlands.[25-29] With continued screening procedures, the prevalence of CRC and EC is going to rise and the direct and indirect costs of treatment are expected to rise. Accordingly, a search for optimizing the CRC and EC management is crucial. By exposing the financial burden of the cancer and by exploring the cost-effectiveness of the new technologies in this patient population, the current studies **(chapters 2,3,4,5, and 6)** provide decision makers with information for health services planning. [30, 31]

Part II of this dissertation suggested that the new technologies such as gum chewing, perioperative enteral nutrition and early oral feeding (**chapters 4, 5 and 6**) are safe and low cost although their cost-effectiveness cannot be demonstrated yet. Usefulness and value of information on cost-effectiveness should be recognized which will help in future decision making process. However further research with methodological improvements are needed to enhance the reliability of economic studies. Decision makers should consider research of such interventions in the management of CRC and EC. Developing (cost) effective interventions to improve treatment outcomes would be worthwhile.

Clinical Practice

Clinicians play a vital role in healthcare spending. It is important that clinicians consider both costs and effects of health interventions and deliver healthcare in cost-effective way. It is therefore important that clinicians understand the role of cost-effectiveness analyses for healthcare delivery and assess the quality of economic evaluations.[32-34]

Our findings provide evidence for clinicians regarding the economic implications of nutritional interventions in CRC and EC patients. The trial-based economic evaluations of SANICS I, SANICS II and NUTRIENT II studies (**chapters 4, 5, 6**) showed that gum chewing, perioperative enteral nutrition and early oral feeding are feasible and simple interventions. Exploring such innovative and inexpensive interventions to reduce postoperative complications might lead to a reduction in healthcare costs. Clinicians should understand this and investigate such interventions in future studies.

7.4. Further research

Several recommendations for further research emerge from this thesis. The search for cost-effective means for reducing the economic and clinical burden of CRC and EC should be fostered and our studies could serve as a basis for incorporating nutritional interventions. More research addressing the nutritional interventions (oral or enteral) at different time points (perioperative, few hours before or after surgery) with or without nasogastric tubes should be explored to study the impact on end points, such as hospitalization, morbidity, mortality, quality of life and its long-term cost-effectiveness. Modelling for long-term quality of life in colorectal and EC patients would also be interesting. A health economic model allows evidence from different sources to be synthesized so that an estimate of the long term costs and outcomes of nutritional interventions could be projected.

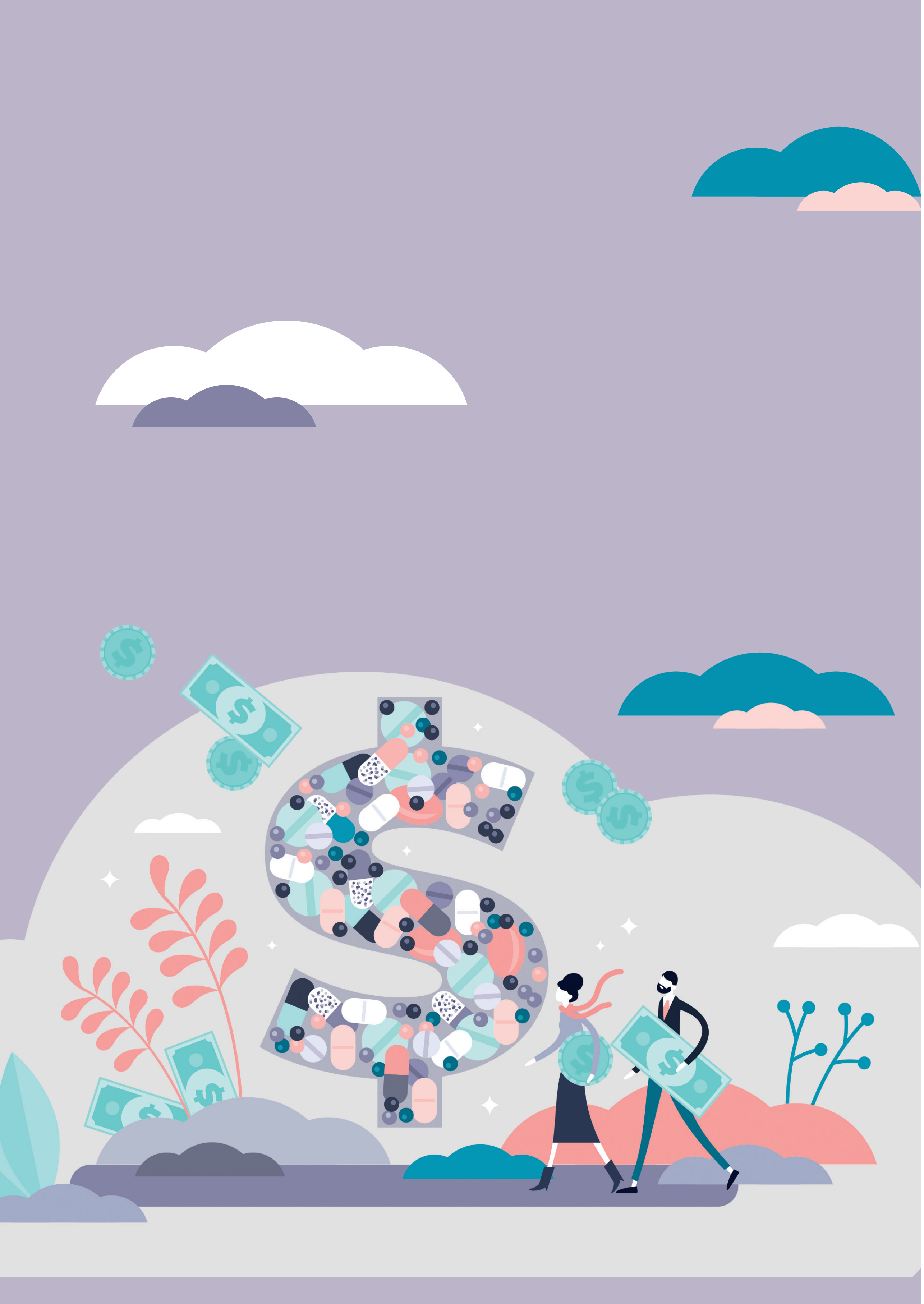
Research involving nutritional interventions is scarce and comparability of economic evaluations is difficult with the currently available literature since they differ in cost estimation methodologies and lack of standardized quality reporting particularly for nutrition related costs and health outcomes. Defining methodological and structural requirements for assessing the cost-effectiveness of nutritional interventions would be extremely worthwhile. To this extent, nutrition economics is a new branch in HTA which has been created by experts in the field of nutrition and health economics to explore and discuss the new guidelines for high quality economic data for nutrition. We support this platform and recommend addressing the methodological issues in the evaluation of nutritional interventions in future research. Furthermore, a collaboration of clinicians, nutritionists and qualified health economists to perform and interpret nutritional economic studies is recommended to achieve the best results.[35]

REFERENCES

1. Peters EG, Smeets BJJ, Nors J, Back CM, Funder JA, Sommer T, et al. Perioperative lipid-enriched enteral nutrition versus standard care in patients undergoing elective colorectal surgery (SANICS II): a multicentre, double-blind, randomised controlled trial. The lancet Gastroenterology & hepatology. 2018;3(4):242-51.
2. Berkelmans GHK, Fransen LFC, Dolmans-Zwartjes ACP, Kouwenhoven EA, van Det MJ, Nilsson M, et al. Direct Oral Feeding Following Minimally Invasive Esophagectomy (NUTRIENT II trial): An International, Multicenter, Open-label Randomized Controlled Trial. Ann Surg. 2019.
3. Sun HB, Li Y, Liu XB, Zhang RX, Wang ZF, Lerut T, et al. Early Oral Feeding Following McKeown Minimally Invasive Esophagectomy: An Open-label, Randomized, Controlled, Noninferiority Trial. Annals of surgery. 2018;267(3):435-42.
4. Rinninella E, Persiani R, D'Ugo D, Pennestri F, Cicchetti A, Di Brino E, et al. NutriCatt protocol in the Enhanced Recovery After Surgery (ERAS) program for colorectal surgery: The nutritional support improves clinical and cost-effectiveness outcomes. Nutrition. 2018;50:74-81.
5. Farkkila N, Sintonen H, Saarto T, Jarvinen H, Hanninen J, Taari K, et al. Health-related quality of life in colorectal cancer. Colorectal Dis. 2013;15(5):e215-22.
6. Ko CY, Maggard M, Livingston EH. Evaluating health utility in patients with melanoma, breast cancer, colon cancer, and lung cancer: a nationwide, population-based assessment. J Surg Res. 2003;114(1):1-5.
7. Farkkila N, Torvinen S, Sintonen H, Saarto T, Jarvinen H, Hanninen J, et al. Costs of colorectal cancer in different states of the disease. Acta Oncol. 2015;54(4):454-62.
8. Hall PS, Hamilton P, Hulme CT, Meads DM, Jones H, Newsham A, et al. Costs of cancer care for use in economic evaluation: a UK analysis of patient-level routine health system data. Br J Cancer. 2015;112(5):948-56.
9. Byun JY, Yoon SJ, Oh IH, Kim YA, Seo HY, Lee YH. Economic burden of colorectal cancer in Korea. J Prev Med Public Health. 2014;47(2):84-93.
10. Boersema GSA, Wu Z, Menon AG, Kleinrensink GJ, Jeekel J, Lange JF. Systemic Inflammatory Cytokines Predict the Infectious Complications but Not Prolonged Postoperative Ileus after Colorectal Surgery. Mediators of inflammation. 2018;2018:7141342.
11. Iyer S, Saunders WB, Stemkowski S. Economic burden of postoperative ileus associated with colectomy in the United States. J Manag Care Pharm. 2009;15(6):485-94.
12. Asgeirsson T, El-Badawi KI, Mahmood A, Barletta J, Luchtefeld M, Senagore AJ. Postoperative ileus: it costs more than you expect. J Am Coll Surg. 2010;210(2):228-31.
13. Mao H, Milne TGE, O'Grady G, Vather R, Edlin R, Bissett I. Prolonged Postoperative Ileus Significantly Increases the Cost of Inpatient Stay for Patients Undergoing Elective Colorectal Surgery: Results of a Multivariate Analysis of Prospective Data at a Single Institution. Dis Colon Rectum. 2018.
14. Atkinson C, Penfold CM, Ness AR, Longman RJ, Thomas SJ, Hollingworth W, et al. Randomized clinical trial of postoperative chewing gum versus standard care after colorectal resection. Br J Surg. 2016;103(8):962-70.

15. Hulscher JB, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, et al. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. The New England journal of medicine. 2002;347(21):1662-9.
16. Goense L, van Dijk WA, Govaert JA, van Rossum PS, Ruurda JP, van Hillegersberg R. Hospital costs of complications after esophagectomy for cancer. Eur J Surg Oncol. 2017;43(4):696-702.
17. Drummond M. Cost-of-illness studies. Pharmacoeconomics. 1992;2(1):1-4.
18. Clabaugh G, Ward MM. Cost-of-illness studies in the United States: a systematic review of methodologies used for direct cost. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2008;11(1):13-21.
19. Hakkaart-van Roijen L, Van der Linden N, Bouwmans C, Kanters T, Tan SS. Kostenhandleiding. Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg In opdracht van Zorginstituut Nederland Geactualiseerde versie. 2015.
20. Freijer K, Lenoir-Wijnkoop I, Russell CA, Koopmanschap MA, Kruizenga HM, Lhachimi SK, et al. The view of European experts regarding health economics for medical nutrition in disease-related malnutrition. Eur J Clin Nutr. 2015;69(5):539-45.
21. Freijer K, Bours MJ, Nuijten MJ, Poley MJ, Meijers JM, Halfens RJ, et al. The economic value of enteral medical nutrition in the management of disease-related malnutrition: a systematic review. Journal of the American Medical Directors Association. 2014;15(1):17-29.
22. al. KFe. Nutrition Economics - An Introduction. ISPOR CONNECTIONS 2014;4:10-11; July/ August 2014.
23. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. BMC Medical Research Methodology. 2017;17(1):162.
24. Peters M, Crocker H, Jenkinson C, Doll H, Fitzpatrick R. The routine collection of patient-reported outcome measures (PROMs) for long-term conditions in primary care: a cohort survey. BMJ open. 2014;4(2):e003968.
25. kankerregistratie N. 2017 [Available from: www.cijfersoverkanker.nl.
26. KWF. https://www.kwf.nl/kanker/dikkedarmkanker/Pages/default.aspx [
27. Ferlay J. Cancer Incidence in Five Continents. Processing of data. IARC Sci Publ. 1992(120):39-44.
28. Incidentie slokdarmkanker [Internet]. KWF. 2020 [cited 28/07/2020]. Available from: https://www.kwf.nl/kanker/kwf-en-slokdarmkanker/Pages/default.aspx.
29. Kankerregistratie N. Prevalentie slokdarmkanker 2018 [Available from: https://www.cijfersoverkanker.nl/selecties/Dataset_7/img5c5949073b787.
30. Eichler HG, Kong SX, Gerth WC, Mavros P, Jonsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2004;7(5):518-28.
31. Brouwer W, van Baal P, van Exel J, Versteegh M. When is it too expensive? Cost-effectiveness thresholds and health care decision-making. The European journal of health economics : HEPAC : health economics in prevention and care. 2019;20(2):175-80.
32. Owens DK, Qaseem A, Chou R, Shekelle P. High-value, cost-conscious health care: concepts for clinicians to evaluate the benefits, harms, and costs of medical interventions. Annals of internal medicine. 2011;154(3):174-80.

33. Bovier PA, Martin DP, Perneger TV. Cost-consciousness among Swiss doctors: a cross-sectional survey. BMC Health Services Research. 2005;5(1):72.
34. Stammen LA, Stalmeijer RE, Paternotte E, Oudkerk Pool A, Driessen EW, Scheele F, et al. Training Physicians to Provide High-Value, Cost-Conscious Care: A Systematic Review. JAMA. 2015;314(22):2384-400.
35. Freijer K, Lenoir-Wijnkoop I, Russell CA, Koopmanschap MA, Kruizenga HM, Lhachimi SK, et al. The view of European experts regarding health economics for medical nutrition in disease-related malnutrition. European Journal of Clinical Nutrition. 2015;69(5):539-45.



ADDENDA

APPENDIX FOR CHAPTERS 2, 3 & 5

Overview of the most important cost categories SANICS II study

Care type	Unit price (in euros; 2015)	Source
Healthcare costs		
Primary care physician/GP	33	Dutch guidelines for costing studies
Specialists per visit	116	Dutch guidelines for costing studies
Paramedic per visit	33	Dutch guidelines for costing studies
Physiotherapy per visit	33	Dutch guidelines for costing studies
Occupational therapist per visit	33	Dutch guidelines for costing studies
Speech therapist per visit	30	Dutch guidelines for costing studies
Exercise therapy	34	Dutch guidelines for costing studies
Dietician per visit	27	Dutch guidelines for costing studies
Psychologist (visit)	94	Dutch guidelines for costing studies
Home care (hour)	73	Dutch guidelines for costing studies
Emergency department visit	259	Dutch guidelines for costing studies
Ambulance transport	613	Dutch guidelines for costing studies
Outpatient visit general hospital	91	Dutch guidelines for costing studies
Outpatient visit surgery	73	Dutch guidelines for costing studies
Outpatient visit neurology	99	Dutch guidelines for costing studies
Inpatient hospital day	476	Dutch guidelines for costing studies
Medication	Variable	www.medicijnkosten.nl
MRI Abdomen	272.34	NZA tariff
MRI Rectum	268.74	NZA tariff
Diagnostic coloscopy	352.48	NZA tariff
Endoscopy	210.08	NZA tariff
CT Thorax	181.44	NZA tariff
CT Abdomen	187.84	NZA tariff
Proctoscopie	86.4	NZA tariff
Appendectomy	234.36	NZA tariff
Kidney dialysis	238.5	NZA tariff
Blood transfusion	324.95	Calculated from hospital records
Bloed test	6.49	NZA tariff
Echocardiogram	118.32	NZA tariff
CT-PET scan	1176.53	NZA tariff
Radiotherapy	1635	
Iron infusion	18.55	NZA tariff
Chemotherapy	188.54	Calculated from hospital records
Revalidation therapy per hour	153	Dutch guidelines for costing studies
Other costs (productivity)		
Absenteeism/presenteeism	34.98	Dutch guidelines for costing studies
Unpaid work	14.09	Dutch guidelines for costing studies

SUMMARY

Colorectal (CRC) and esophageal (EC) cancers are the most prominent and deadly cancers with high morbidity, mortality rates and increased healthcare expenditure. Postoperative complications such as postoperative ileus (POI) and anastomotic leakage (AL) are inevitable and they further reduce the functional capacity and quality of life in these patients.

The escalating clinical and economic burden of CRC and EC coupled with high costs of its management on one hand and limited health resources on the other hand, provide the rationale for fostering the search for cost-effective interventions for managing CRC and EC. Three randomized controlled trials were recently conducted with nutritional interventions such as gum chewing and perioperative enteral nutrition in CRC and early oral feeding in EC. In this dissertation, we provided an overview of cost-effectiveness of these interventions. In addition, the financial burden of CRC and EC, its complications and the quality of life was investigated.

Part I of this dissertation presented two studies conducted to assess the costs and quality of life of CRC and burden of its complications. In **chapter 2,** we explored the societal cost of illness of CRC and its drivers in the Netherlands. Our estimates revealed a 3-month societal cost of €3,211 with 45.5% of this cost attributable to productivity costs highlighting the high financial burden of CRC on Netherlands society and healthcare system. In **chapter 3**, we explored the clinical and economic burden of postoperative ileus using the data from SANICS II trial. It was observed that patients with POI had increased inflammatory parameters, higher costs, lowered functioning, reduced quality of life and utility. When we compared utilities between patients who had only POI with patients without any complications, the effect was much more remarkable. Consequently, it was demonstrated that there is an association between inflammatory markers in blood and postoperative complications and that inflammation is elevated after manipulation of intestine.

Part II of this thesis informed specifically the cost-effectiveness of interventions tested in the new trials (SANICS I, SANICS II and NUTRIENT II). In **chapter 4,** we performed an economic evaluation alongside SANICS I trial and explored whether gum chewing could be a cost-effective intervention and determined its effect on hospital costs and health-related quality of life. Patients in the intervention group were asked to chew gum at least three hours prior to surgery and again three hours after the end of surgery. Patients in control group received placebo dermal patch three hours prior to surgery. Mean costs for ward stay were significantly lower in the gum chewing group however no significant differences were seen in the overall in-hospital costs or utilities. Cost-effectiveness analysis for two postoperative complications POI and AL was determined. Gum chewing was seen to be dominant with lesser costs and more effects in more than 50% of the simulations for both POI and AL.

An economic evaluation was then performed alongside SANICS II trial from a societal perspective as seen in **chapter 5** of this thesis. SANICS II was a multicentre randomized controlled trial conducted in three Dutch and two Danish hospitals. Lipid enriched nutrition was administered just before, during and after the colorectal resection to patients in intervention group and compared to patients in standard care or no nutrition group. Societal costs, quality of life scores and utilities between the two groups did not differ significantly. Cost-effectiveness analysis for global quality of life was determined and it was observed that intervention resulted in an additional cost of €2,699 and a lower quality of life. We also observed that the intervention resulted in an additional cost of €2,941 for a marginal increase in QALY (0.003) suggesting that the intervention was not cost-effective compared to usual care. In **chapter 6**, we assessed the effect of direct oral feeding following minimally invasive esophagectomy on treatment costs and health-related quality of life. This study was performed for the NUTRIENT II trial population. NUTRIENT II was a multicenter prospective randomized controlled trial performed at two hospital units in the Netherlands and one hospital in Sweden. The trial studied effect of early oral feeding in comparison with standard of care (tube feeding) on functional recovery following esophagectomy. We observed that direct oral feeding resulted in similar costs (€26,014 versus €26,989, p=0.825) but significantly reduced the need for home care assistance (48.9%) in comparison with the standard of care group (77.1%), p=0.004. We also observed that patients in the direct oral feeding progressed more quickly/steadily to recovery.

In conclusion, the findings of this dissertation present high quality evidence on economic implications of nutritional interventions in CRC and EC and further provide insights for public health policy makers about the debilitating financial burden of CRC and EC in the Netherlands.

VALORIZATION

Introduction

This chapter discusses the societal value of the results found in this thesis for researchers, patients, healthcare professionals and policy makers. Moreover, the efforts made to disseminate the knowledge gained from this thesis are described.

Colorectal cancer (CRC) and esophageal cancer (EC) are gastrointestinal cancers with high incidence and mortality rates (estimated in the Netherlands at 14,921 incidences and 6,396 mortality cases in colorectal cancer; 2,458 incidences and 2,046 mortality cases in esophageal cancer in 2018).[1] Postoperative complications (such as postoperative ileus and anastomotic leakage after colorectal surgery and anastomotic leakage and pulmonary complication in EC) are inevitable despite advances in surgical techniques and occur in about 30-46% of the patients.[2-7] Postoperative complications are associated with increasing costs and also negatively affect the quality of life.[8] In 2017, the Dutch government spent 597 million euro on CRC (representing 0.5% of the total healthcare costs in the Netherlands) and the Dutch healthcare costs for EC were estimated at 124 million euro in 2007.[9] In this context, it is important to identify cost-effective interventions to reduce economic burden of CRC and EC and the associated complications.

This dissertation had the objective to assess the economic burden of colorectal and esophageal cancer and to estimate the cost-effectiveness of three interventions recently assessed in trial-based economic evaluations.

Relevance for researchers

The findings in this thesis gives details on burden of costs in CRC and EC. This thesis also provides an overview of the current economic evaluations conducted in CRC and EC which indirectly focusses on: First, methodological challenges that were identified in the conduct of trial-based economic evaluations. Missing data and lack of standardization of administration of questionnaires limited the results of some trial-based economic evaluations. Optimization of handling of missing data during the planning stage of a randomized controlled trial (RCT) and involving the patients in their progress and providing them feedback are recommended to increase the response rate and limit the missing data. Furthermore, we recommend inclusion of cost and quality of life questionnaires at several time points to compare the outcomes from baseline to different time points; Second, nutrition as an intervention has some intrinsic challenges due to lack of specific methodology to assess the impact of nutrition on health and health-related quality of life. Cost-effectiveness of medical nutrition is a new area in health economics and performing economic analysis of such interventions without a systematically developed methodology is likely to be inaccurate.[10] Developing new guidelines for better judgement of nutritional interventions is essential.[10, 11]

Relevance for patients and healthcare professionals

This thesis revealed the high burden of postoperative complications on both patients and family of patients with CRC and EC. In particular, this thesis shows, not only which healthcare costs are related to hospital consumption and productivity but also the percentage of reported problems in each dimension (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression). We also show that complications result in higher costs (e.g. postoperative ileus resulted in 38% to 47% higher costs) with lower quality of life not only at 3 months but also at 6 months.

The cost-effectiveness results of the economic evaluation in this thesis concerning two perioperative nutritional methods (perioperative nutritional intervention and gum chewing) were not promising. Perioperative enteral nutrition was more expensive and less or little more effective than the control intervention which led to high incremental cost-effectiveness ratios on the two outcomes (global quality of life and quality-adjusted life years). Although, gum chewing was less expensive and more effective in reducing the postoperative ileus and anastomotic leakage, it remained a challenge to conclude its cost-effectiveness due to limitations in the current data. Evidence in our study showed that direct oral feeding after esophagectomy required less home care and was equally expensive and showed improvement in several outcome measures (e.g. quality of life) however, further research is essential.

The methodological studies described in this thesis are directly relevant to the patients and healthcare professionals. The studies aimed to decrease the complication rate and therefore increase the quality of life in the patients. In addition, it is relevant for patients and healthcare professionals to know what the (cost-) effectiveness of intervention aiming to treat CRC or EC is. Although it is unrealistic to assume that every patient or/and healthcare professional understands the results of the studies in this thesis, it is possible to present the overall conclusion in a comprehensible way.

Relevance for policy makers or healthcare insurance companies

This thesis provides important messages for policy makers (e.g. the Dutch Ministry of Health or healthcare providers) and health insurance organizations (such as 'Zorginstituut Nederland'). Healthcare policy makers are urged to make complex decisions in the context of increasing availability of new and innovative interventions and treatments on one hand, and scarce resources on the other hand. Therefore, it is crucial to provide them with evidence on potential cost-effectiveness of healthcare interventions. Evidence from this thesis provides the healthcare policy makers with the following messages: First on the clinical and economic burden of CRC and EC and of the complications; second on the challenges of nutritional interventions and absence of cost-effectiveness results for such interventions; and third on the significance of a reliable cost-effectiveness analysis with appropriate data collection during RCT.

It is important to look at the (cost-) effectiveness of a treatment for the policy makers and insurance companies to make a decision on what to reimburse. Regarding the SANICS I study, although it was difficult to certainly conclude the cost-effectiveness of gum chewing, reduction in rate of complications reduced the costs for ward stay. The NUTRIENT II trial demonstrated similar total costs and significantly reduced the need for home care assistance. This may make policy makers or healthcare insurance companies willing to investigate further into the perioperative nutritional interventions and which patients are best able to benefit from these interventions.

Dissemination

To simulate the dissemination among fellow researchers, the results of all the five studies described in this thesis are published in international journals. Besides international publications, results of the studies in this thesis have been presented at international conferences such as the European Health Economics Association (EUHEA), 2018 as well as locally at Maastricht University Medical Center, Maastricht and Catharina hospital, Eindhoven (wetenschapsdag 2017). Other intended measures to share the findings of this research are face to face meetings with the knowledge users and communicating the message to the target audience, eg. Social media, websites, journals.

REFERENCES:

1. GCO. 2018 [cited 2018. Available from: https://gco.iarc.fr/today/data/factsheets/populations/528-the-netherlands-fact-sheets.pdf.
2. Spanjersberg WR, Reurings J, Keus F, van Laarhoven CJ. Fast track surgery versus conventional recovery strategies for colorectal surgery. The Cochrane database of systematic reviews. 2011(2):Cd007635.
3. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Br J Surg. 2015;102(5):462-79.
4. van den Heijkant TC, Costes LM, van der Lee DG, Aerts B, Osinga-de Jong M, Rutten HR, et al. Randomized clinical trial of the effect of gum chewing on postoperative ileus and inflammation in colorectal surgery. Br J Surg. 2015;102(3):202-11.
5. Goense L, van Dijk WA, Govaert JA, van Rossum PS, Ruurda JP, van Hillegersberg R. Hospital costs of complications after esophagectomy for cancer. Eur J Surg Oncol. 2017;43(4):696-702.
6. Carrott PW, Markar SR, Kuppusamy MK, Traverso LW, Low DE. Accordion severity grading system: assessment of relationship between costs, length of hospital stay, and survival in patients with complications after esophagectomy for cancer. Journal of the American College of Surgeons. 2012;215(3):331-6.
7. Wang J, Wei C, Tucker SL, Myles B, Palmer M, Hofstetter WL, et al. Predictors of postoperative complications after trimodality therapy for esophageal cancer. International journal of radiation oncology, biology, physics. 2013;86(5):885-91.
8. Short MN, Aloia TA, Ho V. The influence of complications on the costs of complex cancer surgery. Cancer. 2014;120(7):1035-41.
9. Volksgezondheidenzorg.info. https://www.volksgezondheidenzorg.info/onderwerp/dikkedarmkanker/kosten/kosten#node-kosten-van-zorg-voor-dikkedarmkanker [
10. Freijer K, Lenoir-Wijnkoop I, Russell CA, Koopmanschap MA, Kruizenga HM, Lhachimi SK, et al. The view of European experts regarding health economics for medical nutrition in disease-related malnutrition. European Journal of Clinical Nutrition. 2015;69(5):539-45.
11. Freijer K. Nutrition Economics - An Introduction: ISPOR CONNECTIONS 2014;4:10-11; July 2014 [Available from: https://www.ispor.org/member-groups/special-interest-groups/nutrition-economics.

ACKNOWLEDGEMENTS

First of all, I would like to thank all the patients who participated in the clinical trials and shared information by filling questionnaires for research. Your help was indispensable for this thesis.

My deepest gratitude and sincere thanks goes to my supervisors, Mickael, Silvia and Misha for guiding me throughout this journey. It started in the first year of my research master when I wrote a proposal under your supervision. Despite not receiving the subsidy for the proposal, I was able to continue working and subsequently registering as an external PhD. Thus, I have had many years of your guidance and support.

Mickael, you instilled the idea of PhD when I had doubts on how to proceed further after research master. You have been always approachable and quick to answer any queries I had. The calmness you radiated helped me to stay positive even during uncertain times. I always felt more confident after our meetings.

Silvia, You inspired me to choose health technology assessment in my research master and I greatly appreciate it. Thank you for your constructive feedback and your help in conducting this research. You came up with quick solutions to the problems and always steered me in the right direction.

Misha, You provided me an opportunity to work at the Catharina hospital as an intern and further extended your support with SANICS II and NUTRIENT II projects after my internship. This literally paved the way for this PhD. Thank you for introducing me to the world of gastrointestinal surgery and sharing your knowledge with me. Your critical feedback always helped me to improve my focus and achieve better results.

I also like to thank the members of the assessment committee, prof. dr. Milena Pavlova, prof. dr. Wim Groot, prof. dr. Annemie Schols, dr. Mark Nuijten and dr. Karen Freijer for taking your valuable time and reviewing this thesis. Your comments helped me to improve this thesis to a great extent.

Thanks to all my co-authors, especially Boudewijn, Emmeline, and Laura for collaborating with me in various studies. It was a pleasure working with you.

I also like to thank Hannerieke van der Boom for coordinating regularly on Phd activities. Thank you Janet for always helping me to plan meetings, answering my questions patiently and for all the background work during the final stages of my PhD.

My friend, Jko, we shared an office for a short amount of time but we remained constantly in touch. Thank you for patiently answering my endless questions in the past weeks. My paranimfs Olga and Pierre. Olga, you were my buddy since the day 1 of research master. Thank you for the amazing time we spent together, our train journeys, pizza lunches and our endless conversations. Pierre, I say thank you for the amazing time we shared and for always being my friend.

My parents and family back in India, thank you for constantly encouraging me and for always believing in me. You gave me moral support every time I was low. You always respected and encouraged my choices. I love you all!

Finally my family in the Netherlands, my husband, daughter and son. Thank you for your unconditioned love, encouragement, understanding and amazing patience. Without your support, this would have been impossible. You are my greatest strength and you know how much you mean to me.

CURRICULUM VITAE

Madhuri Pattamatta was born on 7 July 1978 in Bengaluru, India. She obtained her bachelor's degree in dentistry at Rajiv Gandhi University of Health Sciences, India in 2002. After this, she worked as an independent dentist in a private dental clinic in India till 2008. In 2008, she left to Netherlands to accompany her husband. She then did several jobs such as medical transcriptionist and dental assistant in Eindhoven, the Netherlands. In 2014, she enrolled for the Health Sciences Research Master at the Maastricht University. She completed her internship at the Catharina hospital, Eindhoven. After this, she continued her work on economic evaluation of clinical trials conducted at the Catharina hospital. In 2016, she was officially registered as a PhD student at Care and Public Health Research Institute (CAPHRI) of the Faculty of Health, Medicine and Life Sciences at the Maastricht University. Her research includes burden of disease, patient-reported quality of life, and health economics of nutrition in surgery.

PUBLICATIONS

Pattamatta M, Fransen LFC, Dolmans-Zwartjes ACP, Nieuwenhuizen GAP, Evers SMAA, Kouwenhoven EA, Det MJ van, Hiligsmann M, Luyer MDP. Effect of direct oral feeding following minimally invasive esophagectomy on costs and quality of life. Journal of Medical Economics. 2020 Dec;(in press). doi: 10.1080/13696998.2020.1859843.

Peters EG, Pattamatta M, Smeets BJJ, Brinkman DJ, Evers SMAA, de Jonge WJ, Hiligsmann M, Luyer MDP. The clinical and economical impact of postoperative ileus in patients undergoing colorectal surgery. Neurogastroenterology & Motility. 2020 Aug;32(8):e13862. doi: 10.1111/nmo.13862.

Pattamatta M, Smeets BJJ, Evers SMAA, Peters EG, Luyer MDP, Hiligsmann M. Quality of life and costs of patients prior to colorectal surgery. Expert Review of Pharmacoeconomics & Outcomes Research. 2020 Mar;20(2):193-8. doi: 10.1080/14737167.2019.1628641.

Pattamatta M, Smeets BJJ, Evers SMAA, Rutten HJT, Luyer MDP, Hiligsmann M. Health-related quality of life and cost-effectiveness analysis of gum chewing in patients undergoing colorectal surgery: results of a randomized controlled trial. Acta Chirurgica Belgica. 2018 Oct;118(5):299-306. doi: 10.1080/00015458.2018.1432742.

Pattamatta M, Evers SMAA, Smeets BJJ, Peters EG, Luyer MDP, Hiligsmann M. An economic evaluation of perioperative enteral nutrition in patients undergoing colorectal surgery (SANICS II study). Journal of Medical Economics. 2019 Mar;22(3):238-244. doi: 10.1080/13696998.2018.1557200.